Pediatric Lyme Neuroborreliosis: Different clinical presentations of the same agent; Single center experience

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Abstract

OBJECTIVES: Lyme disease is a vector-associated infectious disease, caused by the agent, spirochete Borrelia burgdorferi. Neurologic findings are observed in approximately 12% of the cases and termed Lyme neuroborreliosis (LNB). Lyme neuroborreliosis may manifest with different clinical neurologic manifestations.

METHODS: The study was conducted at a tertiary training and research hospital. From January 2014 to September 2015, a total of 75 patients diagnosed with encephalitis, ataxia, Guillain Barre Syndrome (GBS), facial paralysis, acute disseminated encephalomyelitis (ADEM), pseudotumorcerebri were evaluated for inclusion to the study. Among these patients whom investigations of B. burgdorferi antibody IgM and/or IgG ELISA and Western Blot (WB) were detected to be positive, were assessed. Epidemiologic data, tick bite histories, duration of symptoms, clinical findings, radiologic findings, treatment durations and prognosis were investigated.

RESULTS: Totally 7 patients had been treated with the diagnosis of Lyme neuroborreliosis. The mean age was 9.14±4.91 years; duration of symptoms before admission was 8.0±4.50 days; and the duration of antibiotic use was 2.85±0.89 weeks. All patients had received ceftriaxone and intravenous immunoglobulin (IVIG); 3 patients had received plasmapheresis (42.9%) and one patient had received pulse corticosteroid therapy. While the patient with the diagnosis of encephalomyeloneuritis and atypical GBS had partially improved, the other patients were completely cured.

CONCLUSION: In this article, we report pediatric LNB patients. B. burgdorferi should also be considered in patients with atypical or severe neurologic involvement or a history of tick bite; it is known that the prognosis is good with appropriate and early treatment.
INTRODUCTION

Lyme disease is a vector-associated infectious disease, caused by the agent, spirochete Borrelia burgdorferi sensu lato (Halperin 2014). Onset of clinical findings occurs with erythema chronicum migrans, followed by potential spread to other organs. Clinical findings depend on the stage of the disease and are generally considered under three titles, including early localized disease, early disseminated disease and late disease. Neurologic findings are observed in approximately 12% of the cases and termed Lyme neuroborreliosis (LNB) (Koedel et al. 2015). Lyme disease of the nervous system is grouped into two as peripheral or central nervous system involvement. Involvement of the central nervous system may occur in many forms, however cerebral and/or spinal cord parenchymal inflammation is rarely observed. Central nervous system findings include lymphocytic meningitis, cranial neuritis, radiculoneuritis and mononeuropathy multiplex and central nervous system parenchymal involvement (Halperin 2015).

Atypical LNB cases have also been reported among adults (Huisman et al. 1999). However, a gradually increasing number of pediatric atypical LNB cases are reported in the literature. The disease is known to have an atypical course also without neurologic involvement.

In addition, the severity of the disease may vary among different patients. While cerebral imaging may reveal severe lesions, the clinical manifestations may be relatively mild (Khan et al. 2015). Due to the atypical clinical course, Lyme neuroborreliosis may not always be considered; in addition, in a considerable amount of patients, no history of tick bite may be obtained.

In this article, we report atypical pediatric LNB patients, whom we followed between 2014 and 2015 and we aimed to underline the fact that prognosis is good in case of early diagnosis and treatment.

MATERIAL AND METHODS

This retrospective study was conducted at tertiary training and research hospital. From January 2014 to September 2015, all patients diagnosed with encephalitis, ataxia, peripheral facial paralysis, GBS and ADEM, pseudotumor cerebri were retrospectively screened and data from patients, for whom investigations of B. burgdorferi antibody IgM and/or IgG ELISA and Western Blot (WB) were detected to be positive, were assessed. Seven cases of LNB under follow-up are presented below in detail. Demographic characteristics, clinical findings, radiological findings, duration of symptoms, treatment and prognosis are presented in Table 1. The male to female ratio was 5 (71.4%), 2 (28.6%). The mean age was 9.14±4.91 years (min: 2, max:17, median:8). While 4 patients were diagnosed with (Cases 2,3,5,7) GBS (57.1%) (2 of them had upper extremity-onset atypical GBS, Cases 3,5), 2 patients were diagnosed with (Cases 4, 6) cerebellar ataxia (28.6%) and one patient(14.3%) was diagnosed with (Case 1) encephalomyeloradiculo neuritis. Six patients had a normal cranial MRI (85.7%), one patient had a result consistent with ADEM (14.3%). The duration of symptoms before admission was 8.0±4.50 days (min:2, max:15, median:10); duration of antibiotic use was 2.85±0.89 weeks on average (min:2, max:4, median:3). All patients had received ceftriaxone and intravenous immunoglobulin (IVIG) (100%); 3 patients had received plasmapheresis (42.9%) (Cases 1,2, 3) and one (14.3%) patient had received high dose steroid treatment (Case 1).

While the patient with the diagnosis of encephalomyeloneuritis (Case 1) and atypical GB (Case 3) had partially improved, the other patients were completely cured.

CASE PRESENTATION

Case 1

The 6-year-old male patient presented with fever, blurred consciousness and sleepiness, which had started 4 days ago. The patient had no such complaints in the past. On admission, patient was febrile (38.5°C axillary), his respiratory rate was 18/min, arterial blood pressure was 100/60 mmHg; he was unconsciousness,
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He had aimless extremity response to painful stimulus; pupils were isochoric and pupillary light reflex was normal; no abdominal skin reflex can be obtained. Babinski reflex was absent; no meningeal irritation findings were observed. Considering encephalitis, he was admitted to the Pediatric Intensive Care Unit (PICU). Cerebral MRI showed relatively symmetrical, T2A-sequence hyperintense lesions in the proximal site of the cervical cord, pons, mesencephalon, thalamus, basal ganglions, internal and external capsules, periventricular white matter, bilateral frontal and parietal subcortical white matter, and results consistent with ADEM (Figure 1–3). Lumbar puncture was performed and revealed a glucose level of 57 mg/dL, a protein level of 110 mg/dl and the cell count showed 10 lymphocytes per mm3. Treatment with ceftriaxone and acyclovir was started. No growth in blood and CSF cultures was detected. Serologic assessment showed negative Brucella, mycoplasma, chlamydia, EBV, TORCH, ANA, anti-DNA, thyroid antibodies. All metabolic investigations were normal. Lyme antibodies were sent for investigation. Cerebrospinal fluid (CSF) HSV PCR, VZV PCR, enterovirus PCR was negative. Moderate background rhythm irregularity was detected on electroencephalography. Electromyography showed acute motor axonal polyneuropathy (AMAN). The patient was started on treatment with pulse corticosteroid therapy (1 g/day methylprednisolone) for 5 days. At the end of IVIG treatment, the patient underwent plasmapheresis due to the occurrence of sphincter deficiency as a new neurologic finding and the inability to receive abdominal skin reflex. He also received plasmapheresis for 5 sessions. And then he was included in physical treatment program.

The patient was considered to have Lyme-associated encephalomyeloneuritis based on all clinical, neurophysiologic and radiologic findings. After 1.5 months of treatment, the patient was unable to walk without abdominal skin reflex and had no swallowing reflex. Upon observation of an inadequate clinical response at the end of pulse corticosteroid therapy, 0.4 g/kg IVIG was started for 5 days. At the end of IVIG treatment, the patient had no abdominal skin reflex. He was started on treatment with pulse corticosteroid therapy (1 g/day methylprednisolone) for 5 days. At the end of IVIG treatment, the patient underwent plasmapheresis due to the occurrence of sphincter deficiency as a new neurologic finding and the inability to receive abdominal skin reflex. He also received plasmapheresis for 5 sessions. And then he was included in physical treatment program.

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Tab. 1. Demographic and clinical characteristics of the patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient age, sex (years)</th>
<th>Symptoms</th>
<th>Symptoms duration before admission (days)</th>
<th>EMG</th>
<th>Cerebral MRI</th>
<th>Final diagnosis</th>
<th>Treatment</th>
<th>Antibiotic and duration</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>6, male</td>
<td>Fever, unconsciousness</td>
<td>4</td>
<td>AMAN</td>
<td>Normal</td>
<td>Encephalomyeloradiculoencephalitis</td>
<td>Pulse prednol, IVIG, plasmapheresis</td>
<td>Seftriakson, 4 weeks</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>Case 2*</td>
<td>15, male</td>
<td>Difficulty on walking</td>
<td>15</td>
<td>AIDP</td>
<td>Normal</td>
<td>Guillain Barre</td>
<td>IVIG, plasmapheresis</td>
<td>Seftriakson, 4 weeks</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Case 3</td>
<td>7, female</td>
<td>Respiratory distress, fever, unconsciousness</td>
<td>5</td>
<td>AMAN</td>
<td>Normal</td>
<td>Atypical Guillain Barre</td>
<td>IVIG; plasmapheresis</td>
<td>Seftriakson, 3 weeks</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>Case 4</td>
<td>17, male</td>
<td>Gait disturbance</td>
<td>10</td>
<td>Normal</td>
<td>Normal</td>
<td>Cerebellar ataxia</td>
<td>IVIG</td>
<td>Seftriakson, 2 weeks</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Case 5</td>
<td>8, female</td>
<td>Fever, weakness in both hands</td>
<td>2</td>
<td>AMAN</td>
<td>Normal</td>
<td>Atypical Guillain Barre</td>
<td>IVIG</td>
<td>Seftriakson, 2 weeks</td>
<td>Full recovery</td>
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<td>Case 6</td>
<td>2, male</td>
<td>Difficulty walking, tremor</td>
<td>10</td>
<td>--</td>
<td>Normal</td>
<td>Cerebellar ataxia</td>
<td>IVIG</td>
<td>Seftriakson, 2 weeks</td>
<td>Full recovery</td>
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<tr>
<td>Case 7</td>
<td>12, male</td>
<td>Inability to walk, fatigue</td>
<td>10</td>
<td>AMAN</td>
<td>Normal</td>
<td>Guillain Barre</td>
<td>IVIG</td>
<td>Seftriakson, 3 weeks</td>
<td>Full recovery</td>
</tr>
</tbody>
</table>

* Case 2 was published in Journal of Clinical Apheresis in 2015 as case report.

![Fig. 1. T2A-sequence hypertense lesions in the thalamus, basal ganglions, internal and external capsules.](image-url)
help, could sit with support, had an onset of voluntary movements in the distal upper extremity, had an improvement in the sphincter defect and gained total consciousness. In the 3rd month of follow-up, he was able to sit without support, eat without help but was still unable to walk. In the 6th month of follow-up, he was still unable to walk. After a year of treatment, he was totally conscious, was able to speak, his arm movements and muscular strength was 5/5; he had no sphincter defects; he was able to walk with the help of a Walker. The boy is under follow-up by pediatric neurology outpatient clinic and is monitored by physical therapy rehabilitation.

Case 2
The 15-year-old male patient presented with difficulty in walking, which had been present for the last 15 days. He had severe ataxia, dysarthria and incapacity on fingertip test. He had normoactive deep tendon reflexes, and had no sensory loss. His cerebral and posterior fossa MRI images were normal. Lumbar puncture revealed protein (211 mg/dl) or glucose (66 mg/dL), direct examination and staining showed no cells or microorganisms. Collagen tissue diseases, Brucella, HSV, EBV, syphilis, rubella, rubeola, toxoplasma, cytomegalovirus, mycoplasma and anti-thyroid antibodies were negative. Immunoglobulins, lipid profile and vitamin E levels were normal. B. burgdorferi antibodies were sent. Considering post-infectious cerebellitis (IVIG, 400 mg/kg), he was treated for 5 days. B. burgdorferi antibody was detected to be positive by IgM and IgG ELISA and confirmed with Western Blot. Neurologic findings persisted following IVIG treatment. Ceftriaxone treatment was given for 4 weeks; however during the 3rd week, ataxia gradually progressed; weakness in the upper and lower extremities was detected (upper extremity muscular strength: 3/5, lower extremity muscular strength: 4/5), and deep tendon reflexes were decreased.

Case 3
7-year-old girl patient, who had been under follow-up at a tertiary center under the diagnosis of hereditary spastic paraparesis with normal activity and consciousness, normal hand and arm movements but with inability to walk, presented with the complaints of fever, acute respiratory distress, blurred consciousness that has been lasting for 3 days. Her symptoms had started 5 days ago and had gradually progressed. On admission, she overall status was poor, severe scoliosis, and thoracic deformity, sleepy, had inadequate spontaneous respiration, isochoric pupils, normal reflex to light, no DTRs from the low extremity. Her oxygen saturation was 76% in the room air; he had sighs during respiration. She was intubated and transferred to the intensive care unit. Treatment with ceftriaxone was started. Imaging investigations were normal. On the 3rd day of follow-up, she gained consciousness; she was able to follow the instructions; however she had no spontaneous respiration and no upper extremity movements. She responded to verbal instructions through the eye movements. In the patient, who was not considered to have pneumonia based on lung radiography and clinical manifestations and who had no causes to explain the respiratory deficiency, a potential for atypical GBS was considered along with the inability to receive upper extremity reflexes.

Fig. 2. T1 A-sequence hyperintense lesions in the periventricular white matter, bilateral frontal and parietal subcortical white matter.

Fig. 3. T2A-sequence hypertense lesions in the proximal site of the cervical cord.
neuroendocrinology of the upper extremity revealed acute motor axonal polyneuropathy (AMAN). All metabolic investigations were negative. HSV 1, HSV 2, TORCH, EBV, mycoplasma, chlamydia, brucella, thyroid auto-antibodies, ANA, anti-DNA were negative. Lyme antibodies were sent for investigation. LP could not be performed due to severe scoliosis. He was started on 0.4 g/kg IVIG for 5 days. Spontaneous respiration started upon completion of IVIG treatment; however it was still inadequate; voluntary moves were observed in the fingertips. B. burgdorferi IgG ELISA and WB results were positive.

Together with the clinical and neurophysiologic results, the patient was considered to have Lyme-associated atypical GBS. Treatment with ceftriaxone was extended to 3 weeks. The second cure of IVIG was given. After the second cure, the patient's spontaneous respiration started becoming regular and weaning was conducted in the ventilator modes; however the patient didn't tolerate. The patient with no adequate IVIG response also received 5 cures of plasmapheresis. She underwent gradual weaning and he tolerated. She was extubated during the 3rd month of treatment. He started speaking and his arm muscular strength increased to 3/5.

In the 1st year of his follow-up, she has now returned to pre-disease state, she is conscious and able to speak; her distal muscular strength is 2/5 and proximal muscular strength is 3/5.

**Case 4**
The 17-year-old male patient presented to our hospital with the complaints of imbalance upon walking, dizziness and vomiting, which had been present for 10 days. The patient had no such complaints before. His physical examination showed that he was conscious, he had normal muscular tonus and muscular strength, normoactive DTRs, and no pathologic reflexes. Cerebellar tests showed ataxic walking, dystadiadochokinesia and the Romberg test result was positive. Among his investigations, hemogram, blood biochemistry, lipids, immunoglobulins and vitamin E levels were normal. HSV, EBV, CMV, Brucella, mycoplasma, chlamydia, rubeola and rubella antibody were negative. Thyroid auto-antibodies were negative. Brain, diffusion, and whole-spinal MRI results were normal. In the CSF, direct examination showed 3 lymphocyte and normal glucose and protein level. Electroencephalography and EMG results were also normal. The 24-hour urinary copper-seruloplasmin was normal. With respect to paraneoplastic syndrome, there was no neuron specific enolase, abdominal-thoracic CT peculiarities. We learnt from his history that he lived on forested land. *Borrelia burgdorferia* IgM, Ig G ELISA and WB were detected to be positive and treatment with ceftriaxone was started. He was considered to have Lyme-associated cerebellar ataxia.

After 14 days of treatment, the patient started having improvements in his complaints and was discharged. His neurologic examination completely returned to normal during the 2nd month of follow-up.

**Case 5**
The 8-year-old girl presented due to imbalance followed by weakness in both hands, which had started 2 days ago. She had no peculiarity in the familial history or medical history. Her examination revealed an upper extremity muscular strength of 3/5; no upper extremity reflexes could be received; she had no sensory defects, her abdominal skin reflexes were normal; Babinski reflex was normal. Cerebral and spinal MRIs were normal. EMG revealed acute motor axonal polyneuropathy (AMAN). Lumbar punction revealed that, glucose was 60 mg/dL (simultaneous blood sugar: 92 mg/dl), protein was 100 mg/dl. TORCH, EBV, HSV 1, 2, Brucella, mycoplasma, chlamydia, ANA Anti DNA were all negative. In the CSF, HSV PCR, VZV PCR, enterovirus PCR were all negative. *B. burgdorferi* antibody IgM and Ig G samples were sent for investigation. Thereafter, the patient was given 0.4 gram/kg/day IVIG for 5 days. *B. burgdorferi* antibody was detected to be positive by Ig M and Ig G ELISA and WB. She was given two weeks of treatment with ceftriaxone. Based on the clinical and neurophysiologic studies, she was considered to have Lyme-associated atypical Guillain-Barre Syndrome. She was included in physical therapy program. After 2 months, her muscular strength was 4/5; she restored her fine skills, she continued with her normal daily activities; she was able to eat without help. She had complete neurologic improvement in the 1st year of follow-up.

**Case 6**
The 2-year-old male patient was referred to our hospital due to complaints of tremor in the hands and feet, and impaired walking, which had been present for 10 days. We learnt that he had tick bite 3 weeks ago and the tick was removed from the another hospital. Upon presentation, he was conscious, active and had ataxia in the body, difficulty in walking, intentional tremor and disability in fine hand skills. DTR could be received; he had no pathologic reflexes, or meningal irritation findings. His muscular tonus was 4/5 in the lower extremity.

TORCH, EBV, Brucella, thyroid autoantibodies, mycoplasma, chlamydia were all negative, metabolic investigations were normal, lipid panel and vitamin E levels were normal. Lyme antibodies were sent for investigation. Cerebral and spinal MRI results were normal. He was detected to be *B. burgdorferi* antibody positive by IgG ELISA and WB. He was diagnosed with cerebellar ataxia. He was given IVIG at a dose of 400 mg/kg for 5 days. After one month of treatment, his cerebellar ataxia had markedly improved and his neurologic examination results were completely normal.
Case 7

The 12-year-old male presented with complaints of fatigue and inability to walk. We learnt that he had no symptoms other than fever and fatigue, which had lasted 10 days. The physical examination performed on admission revealed that he was conscious; DTRs could not be received in the lower extremity, abdominal skin reflex was positive. Babinski reflex was negative; his upper extremity strength was 4/5 and his lower extremity strength was 2/3. Cervical and spinal MRI findings were normal. TORCH, Brucella, mycoplasma, chlamydia, auto-antibodies were negative. B. burgdorferi antibodies were sent for investigation. He was given IVIG at 400 mg/kg for 5 days. B. burgdorferi antibody was detected to be positive by IgG ELISA and WB. Ceftriaxone was added to treatment. EMG results were consistent with AMAN. His treatment with ceftriaxone was completed to 3 weeks. He was included in physical therapy rehabilitation program. In the 1st month of treatment, his neurologic examination results had markedly improved; however his muscular strength was 4/5 in the lower extremity, and 5/5 in the 3rd month of follow-up.

DISCUSSION

Lyme disease is a disorder, which manifests with a wide spectrum of clinical findings (Shapiro 2014). The third most common organ affected by the Lyme disease is the central nervous system and these effects are observed in 10–15% of the cases. While central nervous system involvement may occur in many forms, the most common form is the lymphocytic meningitis. Cerebral and/or spinal cord parenchymal inflammation (encephalomyelitis) may occur rarely (Halperin 2015).

In the recent years, the increased attention to the diagnosis of neuroborreliosis shows that the disease may manifest with different clinical neurologic manifestations. However, due to the atypical clinical course of the cases, it may not always be easy to consider the presence of the disease. The 7 cases we followed were those, who were at the extreme points in their clinical spectrums. All patients had been given antibiotic treatment after establishment of diagnosis. Two patients with GBS didn’t have a lower extremity onset and had atypical course and upper extremity involvement. These two patients were administered plasmapheresis upon absence of a marked clinical response following IVIG treatment due to respiratory failure. While one patient responded in a dramatic way, the other patient failed to respond markedly. A 6-year-old patient with encephalomyeloneuritis had presented with severe manifestations, was diagnosed based on clinical findings MRI, EMG; and upon failure to receive a response from pulse steroids and IVIG, plasmapheresis was performed, however partial improvement was detected. Reviewing the prognosis in our cases, the 2 patients with cerebellar ataxia were completely cured.

Encephalomyeloneuritis is reported to be a very rare finding in LNB and to be more common in Europe relative to USA (Feder et al. 2007). In the literature, there are case reports of encephalomyeloneuritis resulting from leptospira, HSV Type 1 and CMV (Lepur et al. 2007; Nomura et al. 1997; Chimelli et al. 1990). There is also one case of pediatric meningomyeloradiculitis secondary to LNB, published in the literature (Vânia et al. 2015).

The two studies, investigating the prognosis of LNB cases, are interesting. In a recent study, the prevalence of residual symptoms following treatment in LNB cases was reported to be approximately 28% (Dersch et al. 2015). In our cases, there were residual symptoms in the 12th month of follow-up in 28.5% of the cases. Generally, while patients with cerebellar ataxia were completely cured, a patient with cerebral and spinal involvement and a patient diagnosed with atypical GBS had partial improvement. Lyme encephalomyelitis is known to mostly respond well to appropriate antimicrobial treatment however it is also known that pre-treatment neurologic involvement plays an important role in prognosis (Halperin 2015). All of our patients had received antibiotic treatment. The antibiotic treatment, recommended for neuroborreliosis, is 2 to 4 weeks of intravenous ceftriaxone and most of the patients recover (Bingham et al. 1995). An antibiotic treatment longer than 4 weeks is generally not recommended (Wormser 1997). Treatment with oral doxycycline is quite effective in treatment of Lyme meningitis, cranial neuritis and radiculoneuritis (Halperin 2015).

Case 2 had received plasmapheresis since no improvement was achieved with conventional treatment and the symptoms gradually progressed. This was the first apheresis treatment in a patient with Lyme neuroborreliosis, we reported previously in the literature, and the patient had been completely cured (Çelik et al. 2015). On the other hand, in a study comparing the neurophysiologic assessments of 20 pediatric LNB patients with cranial nerve paralysis or meningoencephalitis and 20 healthy children, LNP patients were observed to have normal intellectual skills, memory and executive functions after the episode (Zotter et al. 2013).

The mechanism of invasion of Borrelia burgdorferi to central nervous system is not clear. Acute neurologic involvement may develop within weeks to a few months after the tick bite and may represent the initial finding of the disease. Direct invasion of the spirochete to the neurons, glia and Schwann cells and the inflammatory response, cytokine secretion, vasculitis and autoimmune mechanisms are involved in the pathogenesis (Rupprecht et al. 2008; Cepok et al. 2003; Tatro et al. 1994; Widhe et al. 2004).

In cases of suspected Lyme disease in the central nervous system, demonstration of the intrathecal antibody production is beneficial in supporting diagnosis. However, if the involvement is limited to peripheral...
nervous system, the test is not applicable. Its sensitivity is unclear even in central nervous system diseases. A negative test result in CSF doesn't rule out the disease (Halperin 2015). In the literature, CSF culture positive results or PCR positive results were demonstrated at a rate of 10–30% (Feder et al. 2007).

In conclusion, B. burgdorferi should also be considered in patients with atypical or severe neurologic involvement or a history of tick bite; it is known that the prognosis is good with appropriate and early treatment.

ACKNOWLEDGEMENTS

Case 2 was published in Journal of Clinical Apheresis in 2015 as case report.

REFERENCES