Optic neuritis as a presenting symptom of *Mycoplasma pneumoniae* infection

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A broad range of neurologic disorders has been described in children infected with *Mycoplasma pneumoniae*, of which encephalitis is among the most common. In contrast, the association between optic neuritis and *Mycoplasma pneumoniae* infection has been rarely described in children. We report a case of a 12-year-old girl who was seropositive for antibodies against *Mycoplasma pneumoniae* and presented with optic neuritis without respiratory symptoms or other neurologic findings.

Key words: children, optic neuritis, *Mycoplasma pneumoniae*.

*Mycoplasma pneumoniae* is a well-known cause of upper and lower respiratory tract infections in children including: pharyngitis, bronchitis, and pneumonia.1 *M. pneumoniae* infection is manifested by a wide spectrum of clinical symptoms (asymptomatic, mild upper respiratory illness, and severe pneumonia).2 Central nervous system (CNS) manifestations are the most frequent extrapulmonary complications of *M. pneumoniae* infection and may be life-threatening.3,4 Previously described neurologic manifestations of *M. pneumoniae* infection include post-infectious leukoencephalitis, acute hemorrhagic leukoencephalitis, Guillain-Barre syndrome, transverse myelitis, brainstem encephalitis, cerebellar ataxia, and central white matter disease.5 Optic neuritis is a rare manifestation of *M. pneumoniae* in pediatric patients. Therefore, this case study documents a rare, but serious complication of childhood *M. pneumoniae* infection. This is the eighth reported pediatric case of optic neuritis due to *M. pneumoniae*.

Case Report

A 12-year-old girl was admitted to our hospital with a 15-day history of headaches, ocular pain, and severe reduction of vision in both eyes. The patient’s medical history indicated that she was previously healthy with no history of a recent exposure to other medications or toxic substances. She had no cough, upper respiratory infection, or fever, and there was no history of trauma. Furthermore, her family medical history was also unremarkable. The vital signs and physical examination were normal. No neurologic deficits or cranial nerve dysfunction were noted, with the exception of the reduced visual acuity.

Her best-corrected visual acuity (BCVA) was light perception in the right eye and 0.15 in the left eye. The intraocular pressure was 14 mmHG in both eyes measured with Goldmann applanation tonometry. A slit lamp examination revealed no obvious inflammation in the anterior chamber or vitreous. The funduscopy examination revealed swollen and hyperemic optic discs in both eyes. Visual field examination revealed total visual field loss in the right eye and partial loss in the left eye (Figs 1A and 1B). Optical coherence tomography (OCT) of the optic nerve head revealed a marked, diffuse increase in the retinal nerve fiber layer (RNFL) thickness. A visual evoked potential study showed severe alterations in the P100 wave latency (left eye: P100=156 ms) and morphology. In contrast, no meaningful answer was obtained in the right eye.
Table I. Characteristics and Clinical Data of Optic Neuritis Associated with *M. pneumoniae* Infection in Children

<table>
<thead>
<tr>
<th>Patient No. Case report</th>
<th>Age (Year)</th>
<th>Sex</th>
<th>Side of optic neuritis/Ophthalmic symptoms</th>
<th>Neurological and other clinical findings</th>
<th>Optic disc changes</th>
<th>Cranial and orbital MRI</th>
<th>Serum anti M pneumonia immunoglobulin</th>
<th>Cold agglutinins</th>
<th>Treatment</th>
<th>Visual recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Candler et al. 20 (2004)</td>
<td>8</td>
<td>male</td>
<td>Bilateral / visual loss</td>
<td>changes in consciousness, loss of speech</td>
<td>None</td>
<td>Normal</td>
<td>Symmetric lesions over the putamen, pallidium, thalamus, and tegmentum; signal on the left optic and cerebellum</td>
<td>Positive (1:10,240)</td>
<td>Positive</td>
<td>Steroids IV + erythromycin</td>
</tr>
<tr>
<td>2. Bae et al. 21 (2011)</td>
<td>7</td>
<td>male</td>
<td>Left/ blurry vision</td>
<td>Sleep tendency</td>
<td>Optic papillitis</td>
<td>Positive (1:2560)</td>
<td>Positive (1:32)</td>
<td>Steroids IV</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>3. Chiang et al. 22 (2014)</td>
<td>8</td>
<td>male</td>
<td>Bilateral / visual loss</td>
<td>None</td>
<td>None</td>
<td>Normal</td>
<td>Positive (+, &gt;75 BU/mL)</td>
<td>None</td>
<td>Steroids IV intravenous immunoglobulin</td>
<td>Normal</td>
</tr>
<tr>
<td>4. Rappoport et al. 23 (2014)</td>
<td>11</td>
<td>Female</td>
<td>Bilateral/ visual loss</td>
<td>Febrile illness</td>
<td>Bilateral optic disc edema</td>
<td>Non-specific periventricular lesions</td>
<td>Positive</td>
<td>None</td>
<td>Steroids IV</td>
<td>Normal</td>
</tr>
<tr>
<td>5. Rappoport et al. 23 (2014)</td>
<td>16</td>
<td>Female</td>
<td>Bilateral/ visual loss</td>
<td>Pneumonia</td>
<td>Bilateral optic disc edema</td>
<td>Multiple brain lesions, ADEM; optic nerve enhancement</td>
<td>Positive</td>
<td>None</td>
<td>Steroids IV + oral roxithromycin</td>
<td>Bilateral mild nasal constriction</td>
</tr>
<tr>
<td>6. Rappoport et al. 23 (2014)</td>
<td>13.5</td>
<td>male</td>
<td>Right/ visual loss</td>
<td>Headaches, gastroenteritis</td>
<td>Right optic disc edema</td>
<td>No brain lesions</td>
<td>Positive</td>
<td>None</td>
<td>None</td>
<td>Mild cecocentral scotoma</td>
</tr>
<tr>
<td>7. Rappoport et al. 23 (2014)</td>
<td>12.5</td>
<td>Female</td>
<td>Right/ visual loss</td>
<td>Febrile illness</td>
<td>Right optic disc edema</td>
<td>No brain lesions</td>
<td>Positive</td>
<td>None</td>
<td>Oral azithromycin</td>
<td>Normal</td>
</tr>
<tr>
<td>8. Our patient</td>
<td>12</td>
<td>Female</td>
<td>Bilateral/ reduction of vision in both eyes.</td>
<td>Headaches, ocular pain,</td>
<td>Bilateral optic disc edema</td>
<td>No brain lesions, bilateral contrast enhancement in all segments of the optic nerve</td>
<td>Positive</td>
<td>Positive</td>
<td>Steroids IV + oral clarithromycin</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Laboratory analyses revealed anormal blood leukocyte count (6740/mm$^3$), serum C-reactive protein (3 mg/L), and erythrocyte sedimentation rate (20 mm/h). The liver, kidney, and thyroid function tests, vitamin B12, folic acid, and serum electrolyte levels were normal. Brain magnetic resonance imaging (MRI) was normal. Magnetic resonance imaging of the orbits showed bilateral contrast enhancement in all segments of the optic nerve (Figs. 2A and 2B). No pleocytosis and normal protein and glucose concentrations were noted on cerebro spinal fluid (CSF) analysis. The CSF did not show oligoclonal banding and the immunoglobulin (Ig) G index was normal. PCR for herpes simplex virus was negative. A chest X-ray was normal. Serologic investigations for autoimmune disease and connective tissue disease (anticardiolipin antibodies, anti-microsomal antibodies, antinuclear antibodies, anti-dsDNA antibodies, autoantibodies against aquaporin 4 (anti-NMO), viral and Lyme serology (Epstein Barr virus [EBV], cytomegalovirus, and herpes simplex Ig M and IgG titers) were all negative. The angiotensin-converting enzyme level was normal in the serum and CSF; however she had high titers of serum _M. pneumoniae_ Ig M and low titers of Ig G with positive cold agglutinins. The patient was diagnosed with optic neuritis-associated _M. pneumoniae_ and treated with intravenous pulse methylprednisolone (1 g/day for 5 days) and clarithromycin (15 mg/kg/day for 14 days).

Her visual acuity began to improve in both eyes after 15 days. The BCVA improved to 1.0 and papil edema regressed in both eyes during follow-up. Her visual fields improved significantly (Figs. 3A and 3B). The OCT analysis is revealed diffuse reduction in RNFL thickness (Figs. 4A and 4B). In the follow up visits RNFL decreased gradually and reached to borderline normal levels. She revealed normal neurologic function, and no further episodes were observed during 13 months of follow-up.
Discussion

Optic neuritis is an uncommon disease in childhood and adolescence. Optic neuritis is characterized by acute or subacute loss of vision, decreased color vision, periorcular pain, central scotoma, and an afferent pupil defect. Although the cause of optic neuritis varies and may be idiopathic, optic neuritis may occasionally occur in association with demyelinating lesions (e.g., MS and neuromyelitis optica), autoimmune disease (e.g., sarcoidosis and systemic lupus erythematosus), infectious and parainfectious causes (e.g., syphilis, tuberculosis, and sinusitis), and post-vaccination immunologic response (e.g., vaccinations against measles and rubella). For the patient in this report, demyelinating diseases were ruled out because the CSF did not show oligoclonal banding, the immunoglobulin (Ig) G index was normal, and the brain MRI revealed no demyelinating lesions.

A positive history of a febrile condition, usually an upper respiratory infection can be elicited in greater than one-third of the children with optic neuritis. Numerous pathogens have been associated with optic neuritis; specifically, viruses that have been implicated in optic neuritis including: measles, mumps, chickenpox, rubella, brucella, pertussis, mononucleosis, and EBV. Based on the detection of initially high titers of serum-specific Ig M and low titers of Ig G, and the subsequent disappearance of Ig M and persistence of Ig G antibodies, the patient was diagnosed with acute \textit{M. pneumoniae} infection. Furthermore, we suggested an association between \textit{M. pneumoniae} infection and optic neuritis in our patient because we did not identify another reason for the cause of optic neuritis.

The pathogenesis of mycobacterial damage in the central nervous system is still poorly understood. There are several mechanisms that could explain neurological complications after \textit{M. pneumoniae} infection. Direct invasion of the CNS, immune-mediated neural injury (autoimmunity, immunosupression, immune complex deposition, thrombosis of vessels) and neurotoxity are the most common prevalent theories. \textit{M. neurolyticum} and \textit{M. gallisepticum} produce a neurotoxin, but no neurotoxin production by \textit{M. pneumonia} has been reported in humans. The isolation of \textit{M. pneumoniae}
from CSF and brain parenchyma confirms the invasion of CNS. On the other hand, postinfectious immune-mediated neurologic disease is defined as an immunologic response against *M. pneumoniae* in the periphery that cross-reacts with central nervous system constituents (i.e. antineuronal antibodies). Brainstem, subcortical lesions, and spinal lesions were considered to result from this autoimmune process. The antigenic similarities between *M. pneumoniae* and brain tissue antigens may explain this injury. The microorganisms do not penetrate the blood-brain barrier. Host autoantibodies directed against normal tissue have been described in the context of *M. pneumoniae* infection. Mycoplasma-related acute transverse myelitis or acute disseminated encephalomyelitis are examples of postinfectious immune-mediated neurologic disease. Biberfeld, et al. described antibodies to lipid-associated brain antigens in patients with *M. pneumoniae* induced 1 CNS disease. Cimolai, et al. reported two patients with neurological disease associated with *M. pneumoniae* infection who had high titers of anticentriolar antibodies. Absence of spinal fluid pleocytosis and rapid recovery of optic neuritis following steroid and anti-mycoplasmal antibiotic therapy suggest a para-infectious immune-mediated process as the predominant mechanism in this child.

Optic neuritis associated with *M. pneumoniae* infection has rarely been mentioned in the literature. After conducting a search of the medical literature using the terms, “optic neuritis,” “child,” and “*M. pneumoniae*,” we identified only seven previously published cases of *M. pneumoniae*-associated optic neuritis in children. Table I presents an analysis of 7 documented cases of optic neuritis associated *M. pneumoniae* from the literature and our patient. In 2004 Candler and co-workers have reported an 8 year old boy patient presented with encephalopathy and optic neuritis with *M. pneumoniae* infection. There was convincing evidence of a preceding *M. pneumoniae* respiratory disease with no evidence of viable *M. pneumoniae* in the CSF in their patient. It was suggested that *M. pneumoniae* infection was the cause of neurologic symptoms. On the other hand in 2011 Bae et al. described an 7 year old boy who developed optic neuritis and ophthalmoplegia following *M. pneumoniae* infection. Interestingly his brain MRI showed extensive symmetric high-signal lesions, involving striatum, midbrain, and pontine tegmentum, right subcortical cerebellar white matter lesions and left optic nerve lesions he has no encephalopathy or neurologic symptoms except optic neuritis. Chiang, et al. reported an 8 year old patient who presented with monosymptomatic visual loss after *M. pneumoniae* infection without papillitis, neurological symptoms and abnormal MRI findings. Recently, Rappoport, et al. have reported 10 children with para-infectious optic neuritis in which an infectious pathogen was identified by serology or culture in 6 of 10 children. The main pathogen was *M. pneumoniae* in 4 of 6 patients (67%). Systemic neurologic manifestations (headache, meningitis, and encephalitis) occurred in 6 children. On magnetic resonance imaging, 4 of 10 children had findings consistent with ADEM and 1 of 10 children had non-specific white matter lesions without clinical encephalitis. However, the patient presented in this paper developed optic neuritis due to *M. pneumoniae* infection despite a lack of other neurologic symptoms, including encephalopathy and respiratory symptoms.

**Conclusion**

Central nervous system involvement is common in patients with *M. pneumoniae* infection. However, optic neuritis is a rare *M. pneumoniae*-related neurologic complication in childhood. Therefore, we recommend that *M. pneumoniae* should be included in the differential diagnosis of any child who presents with optic neuritis, including the absence of respiratory symptoms or other neurologic findings.

**REFERENCES**


