Reversible neurological syndromes with atypical pneumonia

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Abstract

Simultaneous or sequential involvement of lungs is frequently encountered with neurological syndromes like meningoencephalitis, cerebellitis, aseptic meningitis, transverse myelitis, or multiple cranial nerve palsies. However, pulmonary involvement is frequently overlooked when all the attention of physician is diverted to neurological disorder. Prompt and early recognition of such potentially treatable association is required to improve diagnostic and therapeutic outcome. We report six patients presenting with various neurological manifestations like meningitis, meningoencephalitis, and myelits associated with atypical pneumonia. With proper clinical correlation and relevant investigations, all of them were diagnosed in time and had remarkable recovery with appropriate treatment.

Key Words

Aseptic meningitis, cerebellitis, *Legionella pneumophila*, *Mycoplasma pneumoniae*, transverse myelitis

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Ann Indian Acad Neurol 2011;14:127-9

Introduction

Neurological manifestations may be associated with simultaneous or sequential involvement of lung. Chronic diseases like malignancy (42%),[1] HIV (40%), tuberculosis (10%),[2] and sarcoidosis (5%)[3] are leading cause of such associations, but an acute condition due to neglected group of organism causing atypical pneumonia like mycoplasma (0.01–4.8%)[4] and legionella can rarely involve both lung and brain.[5] It is often seen that pulmonary involvement remains unrecognized where as neurological manifestations diverts all the attention of physician. A high index of suspicion is required to recognize coexistence of lung and brain involvement to improve diagnostic and therapeutic outcome, as antibiotics like macrolides, which are not considered at times even by experts as the drug of choice in treating pneumonia can cause remarkable recovery in such patients. We report six patients presenting with various neurological manifestations in addition to pulmonary involvement with proper clinical correlation and investigations; all of them were diagnosed for the underlying etiology and had remarkable recovery with appropriate treatment.

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.82806

Case Report

We analyzed six patients admitted from June 2004 to October 2006 in a large superspeciality centre of North West India with various neurological illnesses, and were subsequently found to have atypical pneumonia. The data analysis of patients with different kinds of pneumonia was not available in the medical wards record data.

The age of patients ranged from 20 years to 80 years, with a mean age of 56.6 years. The male to female ratio was 5:1 [Table1]. All the cases had a hacking cough with scanty sputum production along with moderate grade (38–39.2°C) fever and malaise of about 7–10 days, except for one patient who presented about 18 days after onset of his illness. According to clinical presentation, three patients were diagnosed as having acute psychosis, one each had cerebellar ataxia, meningoencephalitis, and acute paraplegia. On general examination, pharyngeal erythema and cervical lymphadenopathy was present in two patients. Chest examination revealed coarse crepitations in three patients while one patient had aegophony.

One patient who presented about 3 weeks after the onset of illness was on anti- tubercular therapy prior to admission, and his condition was still deteriorating. Rest of the patients were taking various higher antibiotics but showed no response.

All these patients were investigated in detail. Polymorphonuclear leucocytosis was seen in three patients with normal to mildly raised ESR. Two patients showed hyponatremia. The skiagram

Table 1: Clinical profile and investigations of the 6 cases

Age (years)	Neurological Manifestation	X-ray chest	Relevant investigations
55	Disorientation, psychosis, cerebellar ataxia	Peribronchial, dens central infiltrate	PCR for *M. pneumoniae*-positive Csf-98 cells/mm^3 90% lympho sugar-54 mg% Protein-63 mg%
45	Meningoencephalitis	Hilar adenopathy, interstitial infiltrate lower zone	PCR for *M. pneumoniae*-positive Csf-28 cells/mm^3 95% lympho sugar-60 mg% Protein-112 mg% EEG-diffuse slowing
20	Acute transverse myelitis	Middle lobe opacity	PCR for *M. pneumoniae*-positive Csf-35 cells/mm^3 78% lympho Sugar 55 mg% Protein-74 mg% MRI Thoracic spine Hyperintense T_2WI at T3-T4 level
70	Disorientation, headache, drowsiness	Rt. Middle and lower zone opacity	PCR for *Legionella* positive Csf-24 cells/mm^3 82% lympho sugar-56 mg% Protein-68 mg% Hyponatremia S. Na^+ 128 meq/l
80	Incoherence, confusion, drowsiness, coma	Rt. Lower zone infiltrate	PCR for *Legionella* positive Csf-10 cells/mm^3 100% lympho sugar-55 mg% Protein 60 mg% Hyponatremia S. Na^+=130 meq/l
70	Headache, lethargy, psychosis	Peribronchial, central infiltrate, pleural effusion	Cold agglutinin positive Csf-79 cells/mm^3 85% lympho sugar-52 mg% Protein-58 mg%

of chest showed peribronchial central infiltrates in three cases [Figure 1], middle-lobe interstitial infiltrate in two cases, and lower zone infiltrate along with bilateral adenopathy in one case. Pleural effusion was seen in one case. PCR for tuberculosis and HIV were negative. MRI brain was unremarkable, while EEG revealed diffuse slow waves consistent with encephalopathy in one patient who presented with meningoencephalitis. The patient with acute paraplegia had hyperintense signal on T_2-weighted MRI imaging at level of 2nd to 9th thoracic spinal segments suggestive of transverse myelitis [Figure 2]. Cerebrospinal fluid examination was done in all six cases,

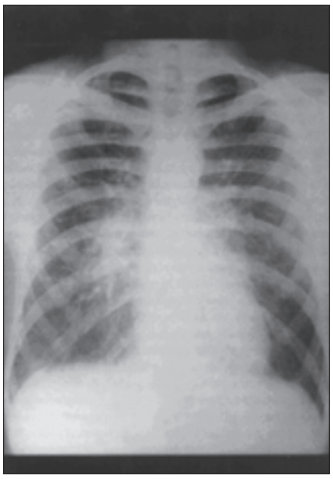

Figure 1: X-Ray chest showing right peribronchial central infiltrate

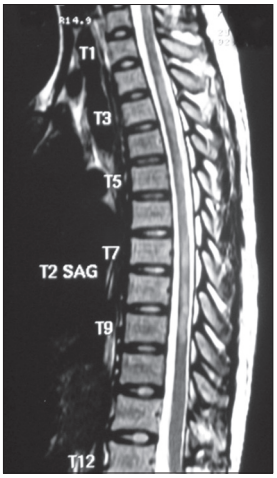

Figure 2: MRI thoracic spine showing T2-weighted hyperintense lesion from T2 to T9 thoracic spinal segments

which showed lymphocytic pleocytosis with raised protein and normal sugar. Possibility of atypical pneumonia with various neurological syndromes were considered and subjected to multiplex PCR in CSF by microchip electrophoresis analysis system.[6] The multiplex PCR was positive for *mycoplasma pneumoniae* in three cases and legionella in two cases. One patient could not afford PCR, hence cold agglutinin test was performed, which was positive.

All patients were started on oral azithromycin 500 mg daily, which was administered for 14 days. They showed signs of clinical improvement within 10 days and had a remarkable recovery over 3–6 weeks with no residual neurological deficits.

Discussion

Mycoplasma pneumoniae and *Legionella pneumophila* are increasingly being recognized as important causes of community-acquired lower respiratory tract infection. Illness usually starts with malaise, fever, headache and sore throat, followed by cough, which may or may not be productive. Examination of chest may

be unremarkable or may have crepitations or wheezes over affected areas. Neurological complications requiring hospital admission occur in 7% of patients.[7]

Patients presented to us with neurological illnesses were found to have atypical pneumonia and a causal relationship was identified. Based on the anecdotal experience, of one of the author's, the association of atypical pneumonia with neurological illnesses and response to macrolide antibiotics both in pulmonary and neurological condition prompted us to investigate these cases for atypical pneumonia.

A wide spectrum of neurologic manifestations has been reported. The most common ones are meningoencephalitis, aseptic meningitis, polyradiculopathy, acute psychosis, cranial nerve palsies, cerebellar ataxia, ADEM, transverse myelitis, and cerebrovascular thromboembolic events or combination of these.[8] Neurological manifestations usually start within few days of respiratory symptoms and can develop as long as three weeks after the onset of respiratory illness. Chest radiographs are often nonspecific with unilateral or bilateral, patchy infiltrate, bronchial or peribronchial in distribution in one or more segment, usually in lower lobe. Upper-lobe involvement and pleural effusion are rare. Other systemic manifestations associated with legionella include diarrhea, high-grade fever and hyponatremia.[9]

Although direct invasion of the respiratory tract is the cause of pulmonary disease, it is unclear whether the same is true for patients with neurologic complications. Three mechanisms have been postulated for the neurological effects. *M. neurolyticum* and *M. gallisepticum* both produce a neurotoxin causing neurological disease in animals, but there is no evidence for a similar mechanism with *M. pneumonia*.[10] Another hypothesis of direct infection has been postulated and *M. pneumoniae* has been isolated from the cerebrospinal fluid using culture or PCR techniques. Growth of *M. pneumoniae* from CSF is notoriously difficult, requiring culture for extended periods in specialized media.[11] However, using rigorous culture techniques, Socan *et al*. were able to culture *M. pneumoniae* from CSF of patients with presumed mycoplasma invasion of the central nervous system.[12] This finding suggests that viable organisms may frequently cross the blood brain barrier thus supporting the direct invasion hypothesis. An autoimmune mechanism might explain the delay often seen between the respiratory and neurological manifestation.[7] Autoantibodies to several host tissues, including brain, have been identified in infected patients with and without neurological complication.[13] Diagnosis rests upon proper correlation of clinical features and isolation of organisms by culture or detection by PCR.[14]

In our cases neurological manifestations like cerebellar ataxia, meningo-encephalitis, transverse myelitis and psychosis with a positive PCR for *M. pneumoniae* and *Legionella*, presence of cold agglutinin (in one patient) and preceding respiratory illness are highly suggestive of the diagnosis of atypical pneumonia associated neurologic dysfunction. Curiously all of our patients responded to macrolide antibiotics without the use of steroids despite one of the mechanisms being autoimmune, thus indicating the direct toxic effect of bacteria / toxins rather than the autoimmune mechanisms for its neurological manifestations.

Conclusions

Atypical organisms have been frequently described and well known to cause lung and brain involvement. However, they need to be essentially recognized because of their potential reversibility and easy to treat with specific use of antibiotics like Macrolides, which have low cost. A high index of suspicion is needed and failure to recognize can be life threatening with a risk of misuse or overuse of nonresponsive antibiotics.

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Received: 11-01-10, **Revised:** 02-04-10, **Accepted:** 30-07-10

Source of Support: Nil, **Conflict of Interest:** Nil