Neurological Complications of Chlamydial Infections: Case Report and Review

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We describe a patient with Chlamydia pneumoniae infection who presented with cerebellar dysfunction, followed by respiratory failure requiring mechanical ventilation. C. pneumoniae is an important respiratory pathogen, and other clinical manifestations, including neurological syndromes, are being increasingly recognized. Meningoencephalitis and other neurological complications have also been described in patients with infections due to Chlamydia psittaci and Chlamydia trachomatis. Chlamydial infections should be included in the differential diagnosis of neurological syndromes, including cerebellar dysfunction.

Neurological complications have been uncommonly reported as manifestations of infections with species of the genus Chlamydia. Chlamydia pneumoniae is being increasingly recognized as an important respiratory pathogen, and other clinical manifestations, including neurological syndromes, have been reported [1-5]. A range of neurological sequelae have been attributed to Chlamydia psittaci [6-24], and Chlamydia trachomatis has been associated with meningonecphalitis [25-29]. We describe a patient with C. pneumoniae infection who presented with cerebellar dysfunction, followed by respiratory failure requiring mechanical ventilation, and we review the literature on neurological complications of chlamydial infections.

Case Report

A 69-year-old woman presented because of a 4-day history of lethargy, anorexia, vomiting, slurred speech, and progressive bilateral incoordination of arms and legs. There was no history of confusion, headache, visual disturbance, seizures, limb weakness, or sensory symptoms. She did not complain of any respiratory or genitourinary symptoms. She was a nonsmoker with a 30-year history of mild scleroderma manifested by Raynaud’s phenomenon, sicca syndrome, and dysphagia, but specific therapy had not been required. Her only medication was nitrofurantoin (50 mg daily) as prophylaxis for recurrent urinary tract infections. There was no history of bird contact.

Examination revealed a temperature of 39.4°C but no tachycardia. She had severe dysarthria but was alert and orientated to time, place, and person. She was grossly ataxic and unable to walk unaided. There was bilateral horizontal nystagmus and other cerebellar signs, including dysdiadochokinesia, intention tremor, and past-pointing; the latter two were bilateral, although more pronounced on the left side. No other abnormalities were detected on cranial or peripheral neurological examination. Examination of the chest revealed coarse crackles in the left upper zone, and chest radiography confirmed left-upper-lobe consolidation.

Initial investigations revealed a hemoglobin level of 12.3 g/dL, a leukocyte count of 11.2 x 10^9/L (64% neutrophils; 29% band neutrophils), and a platelet count of 168 x 10^9/L; the blood film showed neutrophilia and toxic granulations. The serum sodium concentration was 129 mmol/L (reference interval, 135-145 mmol/L), while serum potassium, urea, and creatinine levels were normal. Three sets of standard aerobic and anaerobic blood cultures demonstrated no growth. On the day of admission, a cranial CT scan (precontrast and postcontrast) showed no abnormalities. Microscopy of the CSF showed 4 x 10^6 lymphocytes/L, no polymorphonuclear leukocytes, and no erythrocytes. The CSF protein level was 0.25 g/L, and the glucose level was 5.2 g/L (serum glucose level, 5.0 g/L). Culture of CSF for common bacterial pathogens was negative.

Suspected causative pathogens included Legionella species and Mycoplasma pneumoniae. Treatment was commenced with erythromycin (1 g q6h iv), rifampin (600 mg daily via a nasogastric tube), and ticarcillin/clavulanate (3.1 g q6h iv) to cover the possibility of aspiration pneumonia. The patient became progressively hypoxic within 24 hours of admission, requiring transfer to the intensive care unit, endotracheal intubation, and mechanical ventilation. An MRI scan could not be performed in view of the rapid deterioration. She developed intermittent atrial fibrillation and high-output cardiac failure with low systemic vascular resistance requiring digoxin, dopamine, and noradrenaline infusions. Renal impairment was also evident, with the serum creatinine rising to 168 μmol/L (reference interval, 50-120 μmol/L).

A second chest radiograph revealed progression of the pneumonia, with consolidation of the entire left lung. Bronchoscopy performed on day 3 postadmission revealed a macroscopically inflamed left bronchial tree, and no endobronchial lesion was visible. Culture of bronchoalveolar lavage (BAL) fluid for common bacterial pathogens and Legionella species was negative. Direct immunofluorescence revealed no viral antigens, and no virus was isolated on culture of nasopharyngeal aspirate and
Neurological Complications of Chlamydial Infections: Literature Review

**C. pneumoniae**

*C. pneumoniae* was initially considered to be a strain of *C. psittaci*, known as the TWAR agent; however, it has been subsequently established as a separate species [31]. *C. pneumoniae* is an important human respiratory pathogen, with an antibiotic susceptibility pattern similar to that of *C. psittaci*, and therapy with doxycycline, erythromycin, or other new macrolides is effective [32–34].

The previously reported cases of neurological complications of *C. pneumoniae* infection, all diagnosed on the basis of species-specific serology using the MIF test, are summarized in table 1 [1–5]. There are two reports of meningoencephalitis following respiratory tract infections due to *C. pneumoniae*, both requiring ventilatory support (cases 1 and 5). In case 1, the patient recovered after treatment with corticosteroids and chloramphenicol. There was a fourfold rise in serum IgG titer, and IgM antibody was detected [1].

In case 5 all investigations for routine bacterial and viral pathogens were negative, and the patient recovered after treatment with acyclovir, cefotaxime, and erythromycin. Serum IgM antibody to *C. pneumoniae* was detected on admission, in addition to a high IgG antibody titer, which subsequently declined. IgG and IgM to *C. pneumoniae* were not detected in the CSF, but CSF and throat washings were positive on a direct immunofluorescence test with *C. pneumoniae*–specific monoclonal antibodies [5]. However, the lack of a fourfold rise in the IgG titer and the uncertain value of direct immunofluorescence testing for the detection of *C. pneumoniae* raise some doubt regarding the diagnostic accuracy in this case [35].

The patient in case 4 had lymphocytic meningitis, associated with hepatitis, iritis, and atypical erythema nodosum, which resolved after doxycycline treatment. There was a fourfold rise in IgG titer but no detectable IgM antibody [4].

Cases 2 and 3 involved Guillain–Barré syndrome and lumbo-sacral meningoradiculitis following respiratory tract infections. In case 2 there was a fivefold rise in IgG titer, along with a high IgM titer in both the patient and his brother [2]. In case 3 there was an elevated serum IgM titer, which disappeared by the fifth month, and a serum/CSF antibody ratio that suggested local synthesis of antibodies [3].

**C. psittaci**

Psittacosis or ornithosis is often due to contact with a bird or animal infected with *C. psittaci*. Psittacosis commonly presents as atypical pneumonia, with nonproductive cough, fever, and prominent extrapulmonary features including headache [20, 36–38]. In one series of 135 patients with psittacosis, 87% had a headache, 16% had photophobia, 9% had neck stiffness, and 33% had lumbar punctures performed [38]. In his classic 1880 report, Ritter observed the ‘‘very strong effect on the

Bilirubin, 28 μmol/L (<17), alkaline phosphatase, 70 U/L (30–120), alanine transferase, 70 U/L (7–56), and albumin, 27 g/L (35–45); however, these deteriorated such that by day 7 postadmission the bilirubin value was 151 μmol/L, alkaline phosphatase was 82 U/L, alanine transferase was 306 U/L, aspartate transaminase was 431 U/L, gamma-glutamyl transpeptidase was 11 U/L, and albumin was 15 g/L. In addition, the patient developed coagulopathy with an international normalized ratio of

Antibiotics for the detection of *C. trachomatis* were not detected in the CSF, glucose, 3.9 g/L (serum glucose, 5.0 g/L), and routine bacterial culture was negative. She was weaned from mechanical ventilation after 12 days.

Administration of imipenem/cilastin and erythromycin was continued for 3 weeks, and repeated chest radiography showed clearing of the lung consolidation. The patient’s recovery was complicated by the development of central venous catheter-related coagulase-negative staphylococcal bacteremia and subclavian vein thrombosis requiring anticoagulation. Following a 5-week inpatient stay the patient was discharged, and after a further month of inpatient rehabilitation she had no residual neurological or respiratory abnormalities.

Serum taken on day 2 and day 24 after admission revealed no rise in titers of antibody to influenza A and B, *M. pneumoniae*, *Legionella pneumophila* (serogroups 1–6), *Legionella longbeachae*, or *Legionella micdadei*. Microimmunofluorescence (MIF) assays for *C. psittaci* and *C. trachomatis* did not show rising titers. MIF assay for *C. pneumoniae* (using *C. pneumoniae* antigen obtained from the Washington Research Foundation [Seattle] and the method developed by Wang et al. [30]) demonstrated a >4-fold rise in IgG titer (<1:16 on day 2 to 1:128 on day 24) and a positive IgA titer (1:64 on day 24), but IgM was not detected.

Testing of serum taken 4 months after presentation showed a reduction in IgG titer to 1:32 and a negative IgA titer. Unfortunately, after these results became available, CSF and respiratory specimens could not be retrieved for further investigations such as specific culture, direct immunofluorescence, or PCR to confirm the presence of *C. pneumoniae*.
### Table 1. Summary of data from reported cases of neurological complications due to *Chlamydia pneumoniae*.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Year of report</th>
<th>Patient’s age (y)/sex</th>
<th>Neurological complication</th>
<th>Clinical features</th>
<th>Investigation methods and findings</th>
<th>Serology: findings of MIF for <em>C. pneumoniae</em></th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [1]</td>
<td>1989</td>
<td>16/F</td>
<td>Encephalitis</td>
<td>Respiratory tract infection; 3 d later: unconscious, convulsions, respiratory arrest</td>
<td>CT: cerebral edema; CSF: raised protein level; EEG: focal abnormality</td>
<td>Fourfold rise in IgG and IgM</td>
<td>Chloramphenicol, steroids</td>
<td>Recovery; 1 y later: seizure</td>
</tr>
<tr>
<td>3 [3]</td>
<td>1992</td>
<td>9/M</td>
<td>Lumbosacral meningoradiculitis</td>
<td>Cough, rhinitis; 10 d later: proximal lower-limb weakness, back stiffness, hyporeflexia</td>
<td>CSF: raised protein level; EMG: nerve conduction velocities normal</td>
<td>Fourfold fall in IgM; CSF: total Ig detected</td>
<td>None</td>
<td>Recovery in 6 mo</td>
</tr>
<tr>
<td>4 [4]</td>
<td>1993</td>
<td>37/M</td>
<td>Aseptic meningitis</td>
<td>Fever, headache, chills, muscle tenderness, irritis, atypical erythema nodosum</td>
<td>CSF: lymphocytic pleocytosis</td>
<td>Fourfold rise in IgG, positive IgM</td>
<td>Doxycycline</td>
<td>Recovery in 5 d</td>
</tr>
<tr>
<td>5 [5]</td>
<td>1994</td>
<td>18/M</td>
<td>Meningoencephalitis</td>
<td>Fever, cough, headache, malaise; 10 d later: neck stiffness, double vision, paresthesia, left extensor plantar reflex, unconscious</td>
<td>CT: head normal; CSF: lymphocytic pleocytosis; EEG: generalized abnormality; CXR: pneumonia</td>
<td>Fourfold fall in IgG, positive IgM; CSF negative for IgG, IgM*</td>
<td>Erythromycin, cefotaxime, acyclovir</td>
<td>Recovery in 4 d</td>
</tr>
<tr>
<td>6 [PR]</td>
<td>1997</td>
<td>69/F</td>
<td>Cerebellar ataxia</td>
<td>Fever, malaise, nystagmus, dysdiadochokinesia, ataxia; 3 d later: respiratory failure</td>
<td>CT: head, CSF normal; CXR: pneumonia</td>
<td>Fourfold rise in IgG, rise in IgA</td>
<td>Erythromycin, imipenem/cilastin</td>
<td>Recovery in 3 w</td>
</tr>
</tbody>
</table>

**NOTE.** CXR = chest radiography; EEG = electroencephalography; EMG = electromyography; EPS = electrophysiological studies; MIF = microimmunofluorescence; PR = present report.

* CSF and throat washings were positive on a direct immunofluorescence test with *C. pneumoniae* ±specific monoclonal antibodies.

nervous system” associated with a disease he labelled “pneumomypus” [39]. Meningitis and/or encephalitis has been described in <3% of cases in large series of human psittacosis [20, 37, 38, 40].

Excluding reports of patients with headache alone or where symptoms such as confusion were likely to be due to hypoxia or hypotension [41–46], there are 20 reports of neurological complications due to *C. psittaci*. Diagnosis was made by the *Chlamydia* genus-specific CF test in most cases [6–24]. Twelve cases had clinical features of encephalitis, with fever, confusion, and headache. Cranial nerve palsies, mostly accompanying encephalitis, involve cranial nerves II [12], IV [24], VI [19], and VII [13, 16, 18]. A XIIth cranial nerve palsy has been reported in the non–English language literature [47]. There were also reports of transverse myelitis [20, 25], Guillain-Barré syndrome [14, 17], and cerebellar ataxia [2].

Of the 20 reported cases, 10 involved significant direct contact with birds (3 birds with proven psittacosis; 5 birds were unwell or had recently died), 3 involved vague indirect bird contact, and 7 involved no history of bird contact. Fifteen cases had radiographic or postmortem evidence of pneumonia. Cranial CT was performed in seven cases, and no abnormalities were detected. MRI demonstrated spinal cord abnormalities in one case of transverse myelitis [25]. Examination of CSF revealed lymphocytic pleocytosis in 2 cases, raised protein level only in 5 cases, and no abnormalities in 7 cases. Of the 14 patients treated with tetracyclines or erythromycin, 11 made good recoveries. Two postmortems demonstrated major embolic phenomena [13, 17], a reported complication of endocarditis associated with psittacosis [48].

**C. trachomatis**

*C. trachomatis* causes ocular trachoma (serotypes A to C), genitourinary tract and neonatal infections (serotypes D to K), and lymphogranuloma venereum (LGV, serotypes L1, L2, and L3). Early experimental intracerebral inoculation of the “LGV virus” in animals demonstrated meningoencephalitis [49].
agent was later isolated from CSF during acute human LGV infection, involving no clinical meningoencephalitis or CSF abnormalities [50].

Four cases of meningoencephalitis associated with LGV have been reported [25–27]. However, these cases were reported >50 years ago, when appropriate diagnostic tests for other pathogens may not have been available, and other etiologic agents of meningoencephalitis may have been missed.

Two cases associated with non-LGV serotypes were diagnosed by MIF using pooled C. trachomatis D-K serotypes [28–29]. In one report, the authors claim that high IgG titers suggested systemic infection [29]; however, others state that this elevation may occur with uncomplicated genitourinary infection [51]. C. trachomatis has been implicated in two other cases of meningoencephalitis not described in detail [52, 53].

Discussion

This case highlights the fact that C. pneumoniae infection, like C. psittaci infection, can present with marked neurological features and cause severe pneumonia. Pronounced cerebellar features have been noted in patients with pneumonia due to M. pneumoniae and Legionella species and in one patient with psittacosis [17]. The case described here is, to our knowledge, the first reported case of cerebellar dysfunction as a complication of infection with C. pneumoniae. Other causes of pneumonia reported to cause neurological symptoms (influenza, Mycoplasma, Legionella) were excluded. The patient had a moderately reduced sodium concentration, but this would seem to be an unlikely cause of marked cerebellar ataxia. Neither the results of a CT scan nor later MRI explained the cerebellar findings. The development of acalculous cholecystitis was probably a consequence of severe sepsis; however, a direct effect of C. pneumoniae infection cannot be excluded.

The CF test uses lipopolysaccharide antigen common to all members of the genus Chlamydia and is insensitive for detection of current infection [54, 55]. This test has been used for many years for the presumptive diagnosis of psittacosis. However, infections with C. pneumoniae are more common than psittacosis, and many infections previously diagnosed as psittacosis on the basis of CF testing have been proved to be due to C. pneumoniae by MIF testing [56]. Previously reported neurological complications attributed to C. psittaci on the basis of CF tests, in particular those cases without documented bird contact, may have actually been due to C. pneumoniae.

In this case, the diagnosis of C. pneumoniae infection is strongly suggested by the fourfold rise in titer in the MIF test, which uses species-specific surface antigens contained in the major outer-membrane protein [54]. There was a fourfold rise in IgG titer in addition to a rise in IgA titer, without a rise in IgM titer. This serological profile may represent reinfection with C. pneumoniae. In reinfections, IgM is rarely detected, but an IgA response can be demonstrated [57].

Recent studies have raised concerns about the specificity and sensitivity of using single serum samples for diagnosing active infection with C. pneumoniae [58, 59]. Up to 20% of asymptomatic patients have antibody levels diagnostic of acute infection. In addition, symptomatic patients with C. pneumoniae detected by culture or PCR-EIA often do not have diagnostic antibody titers. These studies emphasize the importance of obtaining properly timed paired sera to observe titer changes.

Unfortunately, currently available diagnostic tests may be unable to accurately diagnose active disease due to C. pneumoniae or to distinguish between infection responsible for respiratory tract disease and that representing carriage of the organism [59]. Direct immunofluorescent testing of respiratory specimens is of limited value, with sensitivity and specificity of <30% those of culture [35]. The significance of C. pneumoniae detected by culture PCR-EIA is also unclear, as the organism has been isolated from healthy persons [58, 59].

In conclusion, we describe a case of C. pneumoniae infection that presented with cerebellar dysfunction. This case and a review of the literature suggest that C. pneumoniae infection, in addition to C. psittaci and C. trachomatis infections, may present with significant neurological manifestations. Chlamydial infections, along with legionella and mycoplasma infections, should be included in the differential diagnosis of pulmonary infections with a neurological presentation.

References
