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Chronic *Chlamydia pneumoniae* Infection: A Treatable Cause of Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS), an elusive and controversial illness, has been a difficult management problem for clinicians. A number of infectious agents have been implicated as the cause of CFS, although consistent and compelling evidence is still lacking [1]. Few well-documented infections could cause persistent inflammatory reaction leading to the symptomatology of CFS [2, 3]. *Chlamydia pneumoniae* is a common cause of respiratory infection and has been demonstrated within plaques of the coronary arteries years after initial infection [4]. Recently demonstrated replication of *C. pneumoniae* within human macrophages and endothelial cells [5] and a potent inducer of proinflammatory cytokines, such as TNF-α and IL-1 [6], raised the possibility of chronic infection that leads to persistent inflammatory response. A previous study failed to demonstrate elevated titers of antibody to *C. pneumoniae* in 50 patients with CFS [7], although fatigue is a common symptom reported by patients for whom sputum cultures are persistently positive for *C. pneumoniae* [8].

Over the past 3 years, we encountered 10 of 171 patients with symptoms of chronic fatigue who had elevated titers of antibody to *C. pneumoniae* long after initial respiratory infection. Most patients had favorable clinical and serological responses to a 1- to 2-months course of azithromycin therapy, although relapse was common. The clinical symptoms of and titers of antibody to *C. pneumoniae* for our 10 patients over the course of treatment are summarized in table 1.

A 32-year-old female developed pharyngitis, cough, cervical lymphadenopathy, low-grade fevers, severe fatigue, and myalgia in January 1993 (patient 1). A medical evaluation showed a normal complete blood cell count and normal results of thyroid function test and serum chemistry analysis. IgG antibody to Epstein-Barr virus was positive. During the following 3 years, the patient had frequent relapses of severe fatigue, diffuse myalgia, night sweats, pharyngitis, headaches, insomnia, and painful, swollen cervical lymph nodes (especially following exertion) that resulted in total disability.

Repeated evaluation in August 1996 revealed small nontender anterior cervical lymph nodes. Results of routine laboratory studies and serologies for several viruses were unremarkable. The titer of IgG antibody to *C. pneumoniae* was 1:256. Magnesium sulfate injections and salt loading failed to alleviate symptoms. One month later, when the patient was having increasing fatigue, the titer of antibody to *C. pneumoniae* rose to 1:1,024. Azithromycin (500 mg) was administered by mouth the first day, followed by

Table 1. Clinical characteristics, titers of antibody to *Chlamydia pneumoniae* at the onset and during antibiotic therapy, and time to decrease in symptoms for patients with symptoms of CFS.

Patient no., age (y)/sex	Symptom(s) and sign(s)	Duration of symptoms (y)	Titer of antibody to *C. pneumoniae*						Time to improvement (w)
			Time of diagnosis	3 mo	6 mo	12 mo	18 mo	21–24 mo	
1, 32/F	CFS, cervical LN	3	⩾1,024	512	128	<8	<8	32	<1
2, 72/F	Fatigue, dry cough, wheezing, sinus pain	1.5	⩾1,024	. . .	32	8	256,* 512†	8	2
3, 28/F	Fatigue, cervical LN, arthralgia	1	256	128	512*	128*	8	32	1.5
4, 36/F	Pharyngitis, cough, fatigue, cervical LN	1	512	. . .	128	. . .	32	. . .	2
5, 54/F	Fatigue, otalgia, pharyngitis, right cervical LN	2	512	128	32	8	. . .	. . .	2
6, 75/F	Fatigue, dry cough, sinus pain	0.5	128	32	32	256*	. . .	. . .	1
7, 57/M	CFS, sinus pain and congestion	2.5	512	128	8	512*	. . .	. . .	2.5
8, 46/M	Fatigue, history of mastoiditis, myalgia	2	128	16	32	. . .	. . .	. . .	1
9, 70/M	Fevers, cough, severe fatigue	0.5	⩾1,024†	16	32	32	. . .	. . .	2
10, 48/M	CFS, sinus pain, hoarseness, mild cough	3.5	⩾1,024†	16	8	8	. . .	. . .	Undetermined

NOTE. Titers are expressed as the reciprocal of the end point dilution of total antibody to *C. pneumoniae* (determined at Specialty Laboratory, Santa Monica, CA). All patients had negative titers of IgM antibody. All assays were performed with calibration standards of known antibody titers. CFS = chronic fatigue syndrome (patients fulfilled the required criteria for the diagnosis of CFS as defined in [1]); LN = lymphadenopathy; . . . = titer not determined.

* Relapse of symptoms.

† Repeated titer after 1 month without treatment. All relapsed patients were subsequently treated with one or more courses of azithromycin.

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250-mg doses for the subsequent 4 days. The patient's condition improved by day 3 of therapy, although her symptoms relapsed 12 days later.

Similar improvement and relapse followed a second 5-day course of azithromycin treatment. Thereafter, 250 mg of azithromycin was given daily for a total of 30 days; this therapeutic course resulted in a marked decrease in her symptoms. She returned to full-time work as a manager at her company and maintained an energy level of 8–9 of 10 for the next 2 years. Follow-up antibody titers are shown in table 1.

Most of our patients had symptoms referable to the upper or lower respiratory tracts, but radiographic studies of the sinuses and chest were unremarkable. Seven of the 10 patients had high levels of total antibody to *C. pneumoniae* 0.5 to 3 years following an episode of symptomatic respiratory infection. Three patients had low antibody titers of 1:128 and 1:256, but their symptoms did decrease with antibiotic therapy. Low or absent antibody response to *C. pneumoniae* was documented for patients with persistently positive respiratory cultures [8]. Comparatively, the mean titers ± SD for 90 controls were 32 ± 36 (range, <8 or 4 to 256). Only two of 19 fatigued patients with reciprocal titers between 32 to 64 responded to 1 month of azithromycin treatment (data not shown).

The spontaneous rise of titers for several patients correlated with an increased severity of fatigue and a concomitant increase in respiratory symptoms. This observation suggests that relapses of symptoms could be due to persistent infection with periodic reactivation rather than reinfection. All of the patients with relapses responded to additional azithromycin treatment.

C. pneumoniae is a common copathogen in patients with respiratory infection [9]. Symptoms of acute purulent sinusitis and mastoiditis in patients 7 and 8, respectively, did decrease after 2–3 weeks of ceftriaxone treatment, but severe fatigue persisted for the next 2 years; fatigue resolved only after 2 months of azithromycin treatment.

Recently, Falck et al. [10] found *C. pneumoniae* DNA in throat secretions from 10 of 11 patients with chronic rhinorrhea, fatigue, and throat biopsies positive for *C. pneumoniae*. Seventy percent of the patients had elevated titers of IgG (1:512) or IgA (1:128) antibody. All of their patients responded to prolonged courses of macrolide therapy, but symptoms frequently recurred.

Collectively, these results suggest that *C. pneumoniae* is an uncommon yet treatable cause of chronic fatigue. The sensitivity, specificity, and interlaboratory variability of the DNA test will need to be better defined. Although seemingly less sensitive and prone to interlaboratory variation, the widely available microimmunofluorescence test may be a practical screening test for this entity before throat biopsy is performed.

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Acute Fever and Petechial Rash Associated with Influenza A Virus Infection

The child with acute fever and petechial exanthem is a challenge to the primary care physician, because several rapidly fatal diseases present in this manner [1]. Of patients with fever and petechiae, 8% to 20% have a serious bacterial infection, and 7% to 10% have meningococcal sepsis or meningitis [2]. Petechial rash illnesses, often with aseptic meningitis, are relatively common manifestations of infections due to several enteroviruses, and these infections usually occur in the summer or fall [1, 3, 4]. Viral exanthems, which occur in the winter and spring, are not uncommon but are rarely petechial [4, 5].

A previously healthy 3-year-old boy was admitted to UCLA Children's Hospital (Los Angeles) in mid-January because of the sudden development of a petechial rash. He had a 3-day history of fever (temperature to 39.7°C), cough, and rhinorrhea. One day before admission, he was treated with trimethoprim-sulfamethoxazole for left otitis media. He received a total of three doses. On the day of admission, his parents noted the petechial rash that was initially on the face but had spread to the trunk and back within hours. There was no history of recent travel or contact with ill persons. He attended day care.

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