

Neurological Involvement in Acute Q Fever

A Report of 29 Cases and Review of the Literature

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Background: Q fever is characterized by its clinical polymorphism; neurological involvement has occasionally been described. In the course of acute Q fever, neurological manifestations may include aseptic meningitis, encephalitis or encephalomyelitis, and peripheral neuropathy.

Objective: To review and evaluate cases of acute Q fever with neurological symptoms diagnosed in our laboratory.

Methods: A total of 1269 acute Q fever cases were recorded from January 1985 to January 2000 in our laboratory and were reviewed for neurological complications. Patients were considered to have acute Q fever when serological procedures showed *Coxiella burnetii* phase II titers of 1:200 or higher for IgG and 1:50 or higher for IgM. Those patients who underwent a lumbar puncture for cerebrospinal fluid analysis or who had abnormal neurological symptoms were selected for this study. We describe the clinical, epidemiological, and biological fea-

tures of these cases. We also review the literature and compare our cases with those previously reported.

Results: Among the 45 patients selected, 14 were excluded because they had normal cerebrospinal fluid and no neurological symptoms. Two were excluded because there were no clinical or epidemiological data. Three major clinical syndromes were observed: meningoen- cephalitis or encephalitis in 17 cases; meningitis in 8; and myelitis and peripheral neuropathy in 4. Encephalitic signs were not specific, but behavior or psychiatric disturbances were common.

Conclusions: Q fever should be included in the differential diagnosis of acute neurological disease in a patient with a fever. Serological testing should be performed in cases of meningoen- cephalitis, lymphocytic meningitis, and peripheral neuropathy, including Guillain-Barré syndrome and myelitis.

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Q FEVER IS A worldwide zoonosis caused by *Coxiella burnetii*, a strictly intracellular organism living in the phagolysosomes of the host cell. Throughout the world, the most common reservoirs for *C burnetii* are cattle, sheep, and goats.¹ Infection in animals is not usually apparent, but the organism is found in urine, feces, milk, and the afterbirth or aborted products of infected animals.² Pets have also been involved, mainly cats but also dogs.³ Moreover, as *C burnetii* can be transported by the wind, a substantial proportion of patients have reported no direct contact with animals.⁴ Human infection occurs following inhalation of contaminated aerosols or ingestion of raw milk or fresh goat cheese. A percutaneous route and vertical transmission from mother to child have also been documented.

A main characteristic of *C burnetii* infection is clinical polymorphism. Q fever

is commonly categorized into acute and chronic forms, and the clinical manifestations, serological profiles, and treatments for the 2 forms are different. Half of acute cases are asymptomatic. The most common clinical syndromes of acute fever are a self-limited febrile illness, a flu-like syndrome, or pneumonia.² Granulomatous hepatitis may occur in association with an increase in liver enzyme levels. Cases of prolonged fever, febrile eruption, myocarditis, and pericarditis have also been reported. While the involvement of the central nervous system (CNS) due to embolism from an infected valve during chronic Q fever endocarditis is common,⁵ neurological symptoms in acute Q fever have been reported less frequently, and their incidence is probably underestimated. To our knowledge, only 17 well-documented cases of meningoen- cephalitis,⁶⁻²² 2 of Guillain-Barré syndrome,^{23,24} 4 of peripheral neuritis,^{25,26} and 6 of aseptic meningitis have been

PATIENTS AND METHODS

PATIENT CHARACTERISTICS

Our laboratory is the French National Reference Center for Rickettsial Diseases in Marseille, France, which receives 9000 samples annually from France and other countries. A total of 1614 Q fever cases were recorded from January 1985 to January 2000 (1269 acute and 345 chronic infections); for most of these, clinical information was available. Case records of patients with acute Q fever were reviewed for neurological complications. Patients with meningitis (cerebrospinal fluid [CSF] pleocytosis), encephalitic and/or medullar involvement, and/or peripheral neuropathy were selected for this study. A headache was considered a neurological symptom when it was severe enough to prompt a lumbar puncture. However, of the cases where a lumbar puncture was performed, we eliminated those where CSF was normal (cell count, $<5/\mu\text{L}$; protein level, $<0.5\text{ g/L}$; and CSF glucose level, half the blood glucose level) and there were no neurological symptoms. Exposure factors, age, sex, presence of immunodepression, clinical presentation (occurrence of fever, pneumonia, or hepatitis), and biological data such as increased erythrocyte sedimentation rate ($>20\text{ mm/h}$), elevated liver enzyme levels ($>40\text{ IU/L}$, which is twice the upper normal value), and thrombocytopenia (platelet count, $<130 \times 10^9/\text{L}$) were studied.

DIAGNOSTIC PROCEDURES

Titers of IgG, IgM, and IgA antibodies in serum samples from each patient were estimated by using the indirect immunofluorescent antibody test as previously described.³³ Serum IgG antibodies were systematically removed before titration of IgA and IgM to avoid rheumatoid factor inter-

ference (RF Absorbent, Dade Behring GmbH, Marburg, Germany). Patients were considered to have acute Q fever when serological procedures showed a *C burnetii* phase II titer of 1:200 or higher for IgG and 1:50 or higher for IgM.³³

Blood-CSF barrier permeability was evaluated by the albumin quotient (plasma albumin level divided by the CSF albumin level; an index of 0.0075 was considered the normal upper limit value).⁹ *Coxiella burnetii* antibody levels were estimated in CSF by immunofluorescence, and intrathecal synthesis of immunoglobulin was evaluated by IgG index (the ratio of CSF antibody titer divided by serum antibody titer to CSF albumin level divided by serum albumin); a ratio higher than 0.8 was considered suggestive of intrathecal synthesis.⁹

Blood and CSF samples (when available) were inoculated onto human fibroblasts grown on a coverslip within a shell vial as previously described.³⁴ After 7 days of incubation at 37°C, cultured bacteria were detected by using the direct immunofluorescence test incorporating rabbit monoclonal antibody to *C burnetii*.³⁵

DNA was extracted from CSF and/or blood samples by using the QiAmp Tissue kit and the QiAmp Blood kit (QIAGEN GmbH, Hilden, Germany) according to the manufacturer's instructions. These extracts were used as templates in polymerase chain reaction amplifications as previously described.³⁶

REVIEW OF THE LITERATURE

We reviewed the English- and French-language literature on MEDLINE for all cases of Q fever with neurological complications from 1946 to 2000 using the following keywords: acute Q fever; *Coxiella burnetii*; neurological involvement; meningoencephalitis; encephalitis; meningitis, Guillain-Barré syndrome; neuritis; and myelitis.

reported.²⁶⁻²⁹ Neurological manifestations described in the course of the acute disease include aseptic meningitis, encephalitis or encephalomyelitis, toxic confusional states, extrapyramidal signs, dementia, behavioral disturbances, and multiple cranial nerve involvement.³⁰ Our laboratory has recently reported the clinical and epidemiological features of 1614 cases of acute and chronic Q fever, including neurological involvement in cases of acute infection, without detailing cases reported or comparing them with cases from the literature.³¹

We report herein 29 cases of Q fever with diverse neurological symptoms from a series of patients diagnosed in our laboratory between January 1985 and January 2000, including 5 previously reported cases of meningoencephalitis.³² The prevalence of neurological complications during acute Q fever was calculated. Neurological manifestations associated with chronic Q fever were excluded. We also reviewed the literature for all cases of acute Q fever with neurological involvement, and their epidemiological and clinical features were compared with our cases.

RESULTS

Between January 1985 and January 2000, the diagnosis of acute Q fever was confirmed in 1269 patients. Forty-

five patients (3.5%) with acute Q fever had a headache, meningeal syndrome, and/or abnormal encephalitic or myelitis signs. Among these, 14 patients with normal CSF were excluded from the study and were considered to have meningeal irritation. We were not able to obtain epidemiological or clinical information for 2 patients, and these 2 were therefore also excluded.

All patients had significant titers of antibodies against *C burnetii* phase II antigens, and none had serological evidence of chronic Q fever. Among the 10 patients tested for the presence of specific CSF antibodies, 6 tested positive (with significant levels of CSF IgG $>1:200$ by immunofluorescence), and 1 of these also had IgM antibodies. The albumin quotient showed a damaged blood-CSF barrier in 5 cases. The IgG index was above 0.8 for 3 patients, but 2 had a damaged blood-CSF barrier. Thus, the IgG index was suggestive of intrathecal synthesis of *C burnetii* antibodies in only 1 case. Attempts to isolate *C burnetii* from blood in 2 cases and from CSF in 5 cases where CSF was abnormal were unsuccessful. Molecular detection in CSF produced negative results in the 3 cases where it was carried out. Bacterial cultures of blood and CSF (including for *Mycobacteria*) were negative, and attempts to isolate herpesvirus and enterovirus failed. The serological assay findings for *Brucella*, *Leptospira*, *Salmonella*, *Bor-*

Table 1. Epidemiological, Clinical, and Biological Data of Patients With Q Fever Meningoencephalitis From Present Study*

Characteristic	Patient No. Sex/Age, y																
	1 M/40	2 F/27	3 M/56	4 M/36	5 M/20	6 M/15	7 M/31	8 M/30	9 F/26	10 F/83	11 M/70	12 M/16	13 M/58	14 M/67	15 M/42	16 M/31	17 F/22
Presence of exposure factors†	+	-	+	+	-	+	+	+	+	-	-	+	-	+	+	-	-
Pulmonary syndrome	-	-	-	-	-	-	+	-	-	+	-	-	+	-	-	-	-
Fever	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+
Severe headache	+	+	-	-	+	+	-	+	+	-	+	+	+	-	-	+	-
Meningeal syndrome	-	+	-	-	-	+	-	+	-	-	+	+	+	-	-	-	-
Confusion and/or somnolence	+	+	+	-	+	+	+	-	-	+	+	+	+	-	+	-	+
Psychiatric symptoms	+	+	-	-	-	-	-	-	-	+	-	+	-	-	+	+	-
Seizures	-	-	-	-	+	-	-	-	-	-	-	+	+	-	-	+	+
Focal neurological deficit	+	+	+	+	-	+	-	-	+	+	-	+	-	+	+	-	+
Complete recovery	+	+	+	+	+	+	+	+	+	-	-	-	+	-	+	+	-
Death	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-
ESR >20 mm/h	-	+	-	+	-	+	+	+	+	+	-	-	ND	ND	+	+	+
Abnormal liver function test‡	-	-	-	+	-	-	-	+	-	-	+	-	-	ND	-	+	+
Thrombocytopenia§	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	+
CSF pleocytosis	+	+	+	-	+	+	-	-	+	ND	+	+	+	+	+	+	-
Phase II antibodies in CSF¶	-	+	+	-	ND	ND	+	+	+	ND	ND	ND	ND	-	ND	ND	ND
Abnormal brain imaging	-	-	-	-	+	+	-	-	-	ND	-	-	-	-	+	-	+
Abnormal EEG	+	+	+	+	+	+	+	-	+	ND	+	+	-	-	+	+	+

*ESR indicates erythrocyte sedimentation rate; CSF, cerebrospinal fluid; EEG, electroencephalogram; plus sign, positive findings; minus sign, negative findings; and ND, study not done.

†Exposure factors include living in rural area, having contact with farm animals or parturient cats, and ingestion of raw milk.

‡Aspartate aminotransferase and/or alanine aminotransferase levels >40 U/L.

§Platelet count <130 × 10⁹/L.

||Defined as a cell count ≥5/μL and protein level ≥0.5 g/L.

¶*Coxiella burnetii* phase II IgG titer ≥1:200.

relia burgdorferi, human immunodeficiency virus, herpesvirus, and enterovirus were negative.

Epidemiological, clinical, and biological data for the reported cases are summarized in **Tables 1, 2, 3, and 4**). Among the 29 patients, 22 were male and 7 were female (male/female sex ratio, 3.1). The mean age was 46.5 ± 20.6 years (range, 7-83 years). No immunocompromised situation was noted. Fourteen patients had a strong epidemiological risk of Q fever because they were in close contact with goats or goat products. Several exposure factors were identified: living in rural areas in 13 of 25 cases; profession (farmer, veterinarian, or shepherd) in 6 of 26 cases; contact with farm animals, specifically goats, or parturient cats in 13 of 23 cases; and ingestion of raw milk or farm goat cheese in 4 of 13 cases.

Clinically, 26 patients were febrile and 12 had myalgia or arthralgia. Nine of the 27 patients had a flulike syndrome, and 3 had pneumonia. Platelet counts were low in 6 cases, and the erythrocyte sedimentation rate was abnormal in 17. There were abnormalities of liver function tests in 8 cases. As for prognosis of the 29 patients, 2 with meningoencephalitis died (Table 1, patients 10 and 11): an

83-year-old woman and a 70-year-old man. Both had severe and diffuse encephalitic signs, and in patient II the findings of a computed tomography (CT) brain scan were normal. Patient 10 was treated with clavulanic acid- amoxicillin and patient 11 with rifampin. Neurological sequelae were noted in 4 of 29 patients (Table 1, patients 12, 14, and 17; Table 3, patient 1). These consisted of a palsy of nerve VI in 1 case, a central vestibular vertigo in 1, a pyramidal syndrome in 1, and a bilateral facial palsy in 1. Two of these patients were treated with doxycycline, 1 with rifampin, and 1 with ciprofloxacin. Twenty-three patients recovered within days or weeks (maximum of 3 months). The course of clinical symptoms showed that, as in patients 1 and 2, neurological aggravation periods lasted from a few hours to a few days, alternating with complete or partial recovery periods. Recovery seemed to occur regardless of treatment. Treatments included erythromycin (2 cases), ampicillin (3 cases), doxycycline (10 cases), pefloxacin (3 cases), and rifampin (5 cases).

Three major syndromes were observed: meningoencephalitis or encephalitis in 17 patients, meningitis in 8, and myelitis and polyradiculoneuritis or peripheral neu-

Table 2. Epidemiological, Clinical, and Biological Data of Patients With Q Fever Meningoencephalitis Found in Literature Review*

Characteristic	Sawaishi et al ⁶	Scully et al ⁷	Ferrante and Dolan ⁸	Guerrero et al ⁹	Casalino et al ¹⁰	Diaz Ortuno et al ¹¹	Cameron et al ¹²
Patient No./sex/age, y	18/M/9	19/M/18	20/M/51	21/M/25	22/M/50	23/F/51	24/F/48
Presence of exposure factors†	+	-	+	-	+	NA	NA
Pulmonary syndrome	-	+	-	-	-	+	+
Fever	+	-	-	+	+	+	+
Severe headache	+	+	+	+	+	-	+
Meningeal syndrome	-	-	-	+	+	-	-
Confusion and/or somnolence	+	-	-	+	+	-	-
Psychiatric symptoms	-	-	+	-	+	-	-
Seizures	-	-	-	-	+	-	-
Focal neurological deficit	+	+	+	+	+	+	+
Complete recovery	+	+	+	+	+	-	-
Death	-	-	-	-	-	-	-
ESR >20 mm/h	+	-	-	+	-	ND	ND
Abnormal liver function test‡	+	-	-	+	-	ND	ND
Thrombocytopenia§	-	-	-	-	-	ND	ND
CSF pleocytosis	+	+	+	+	+	-	-
Phase II antibodies in CSF¶	ND	+	+	+	+	-	-
Abnormal brain imaging	+	-	-	-	-	-	-
Abnormal EEG	ND	+	ND	+	+	ND	-

*ESR indicates erythrocyte sedimentation rate; CSF, cerebrospinal fluid; EEG, electroencephalogram; plus sign, positive findings; minus sign, negative findings; ND, study not done; and NA, not applicable.

†Exposure factors include living in rural area, having contact with farm animals or parturient cats, and ingestion of raw milk.

‡Aspartate aminotransferase and/or alanine aminotransferase levels >40 U/L.

§Platelet count <130 × 10⁹/L.

||Defined as a cell count ≥5/μL and protein level ≥0.5 g/L.

¶*Coxiella burnetii* phase II IgG titer ≥1:200.

Table 3. Patients With Polyradiculoneuritis, Peripheral Neuritis, and Myelitis During Acute Q Fever*

Characteristic	Present Study, Patient No./Sex/Age, y				Other Studies, Patient No./Sex/Age, y		
	1/M/23	2/F/54	3/M/73	4/M/53	Alajouanine et al ²³ 5/F/61	Reilly et al ²⁵ 6/M/32	Bernard et al ²⁴ 7/F/42
Presence of exposure factors†	+	+	+	+	NA	NA	+
Pulmonary syndrome	-	-	-	-	-	-	-
Fever	-	+	+	+	+	NA	+
Severe headache	+	+	-	-	-	NA	-
Meningeal syndrome	+	+	-	-	-	NA	-
Focal neurological deficit	+	+	+	+	+	+	+
Facial nerve involvement	+	-	+	-	+	-	+
Complete recovery	-	+	+	+	+	-	+
Death	-	-	-	-	-	-	-
ESR >20 mm/h	-	+	+	+	-	ND	+
Abnormal liver function test‡	+	+	ND	-	+	+	+
Thrombocytopenia§	-	+	-	+	-	-	-
Phase II antibodies in CSF	+	-	ND	-	ND	ND	-

*ESR indicates erythrocyte sedimentation rate; CSF, cerebrospinal fluid; plus sign, positive findings; minus sign, negative findings; ND, study not done; and NA, not applicable.

†Exposure factors include living in rural area, having contact with farm animals or parturient cats, and ingestion of raw milk.

‡Aspartate aminotransferase and/or alanine aminotransferase levels >40 U/L.

§Platelet count <130 × 10⁹/L.

||*Coxiella burnetii* phase II IgG titer ≥1:200.

ritis in 4. Among those patients with meningoencephalitis (Table 1, patients 1-17), encephalitic symptoms varied. Symptoms included abnormalities of behavior or psychiatric problems (6/17; 35%), confusion and/or somnolence (12/17; 71%), seizures (5/17; 29%), and focal neu-

rological deficit (11/17; 765%). Cerebrospinal fluid was abnormal in 12 cases, with pleocytosis characterized by a predominance of lymphocytes in the CSF in 11 cases and an increased protein level in 1. The glucose level was normal in all cases.

Shaked and Samra ¹³	Marrie ¹⁴	Schuil et al ¹⁵	Brooks et al ¹⁶	Gomez-Aranda et al ¹⁷	Haegy et al ¹⁸	Schwartz ¹⁹	Decourt et al ²⁰	Gallagher ²¹	Powell ²²
25/F/21	26/M/35	27/M/59	28/M/34	29/F/7	30/F/79	31/M/40	32/M/29	33/M/46	34/M/NA
NA	NA	+	-	NA	NA	+	+	+	NA
-	+	-	+	-	+	+	+	-	-
+	+	+	+	+	+	+	+	+	+
+	-	-	-	-	-	-	-	-	+
+	+	-	-	-	-	-	-	-	+
+	-	-	+	+	+	+	+	-	+
-	+	-	+	-	-	+	-	-	-
-	-	-	+	-	-	-	-	-	+
+	-	+	-	+	+	-	+	+	+
+	+	-	+	+	+	+	-	+	+
-	-	-	-	-	-	-	-	-	-
+	-	ND	+	+	+	+	+	+	ND
-	+	ND	-	+	-	+	-	+	ND
-	-	ND	-	-	-	-	-	-	ND
+	+	+	+	-	+	-	-	+	-
ND	-	ND	+	ND	+	ND	ND	ND	ND
-	-	+	-	+	ND	-	ND	ND	ND
+	+	ND	+	+	ND	+	+	+	ND

Table 4. Patients With Meningitis During Acute Q Fever*

Characteristic	Present Study, Patient No./Sex/Age, y								Leng-Levy et al, ²⁷ Patient No./ Sex/Age, y	
	1/M/8	2/M/43	3/M/62	4/M/37	5/F/25	6/F/37	7/F/26	8/M/28	9/F/22	10/M/54
	Presence of exposure factors†	+	-	NA	+	NA	NA	NA	+	+
Pulmonary syndrome	-	-	-	-	-	-	-	-	-	-
Fever	+	+	+	+	+	+	+	+	+	+
Severe headache	+	+	+	-	+	+	+	+	+	+
Meningeal syndrome	+	+	+	+	-	+	+	+	+	+
Confusion and/or somnolence	+	-	-	-	-	-	-	-	-	+
Complete recovery	+	+	+	+	+	+	+	+	+	+
Death	-	-	-	-	-	-	-	-	-	-
ESR >20 mm/h	-	+	+	-	-	+	-	+	-	-
Abnormal liver function test‡	-	-	+	-	-	-	-	-	-	+
Thrombocytopenia§	-	-	-	-	-	-	-	-	-	-
CSF predominantly lymphocytes	+	+	+	+	-	-	+	+	+	-
Phase II antibodies in CSF	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

*ESR indicates erythrocyte sedimentation rate; CSF, cerebrospinal fluid; plus sign, positive findings, minus sign, negative findings; ND, study not done; and NA, not applicable.

†Exposure factors include living in rural area, having contact with farm animals or parturient cats, and ingestion of raw milk.

‡Aspartate aminotransferase and/or alanine aminotransferase levels >40 U/L.

§Platelet count <130 × 10⁹/L.

||*Coxiella burnetii* phase II IgG titer ≥1:200.

Computed tomography brain scans were abnormal in 3 (21%) of 14 cases, with nonspecific diffuse brain edemas in 2 cases and pseudonecrotic edemas in the right temporal area in the third case. Magnetic resonance imaging

(MRI) confirmed on these 2 patients diffuse cerebral edemas. In another case, a CT brain scan was normal, but a brain MRI demonstrated bilateral periventricular edemas (**Figure**). The electroencephalogram carried out in 16

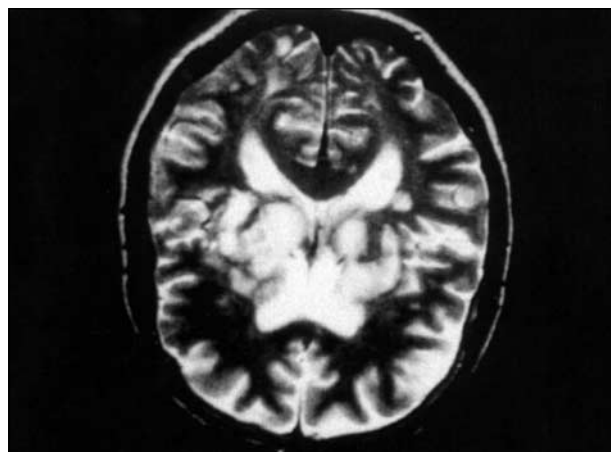
cases revealed abnormalities in 13. These included diffuse encephalitic involvement with right temporal theta (θ) waves or postseizure waves.

Two patients had myelitis (Table 3, patients 2 and 4) with a motor weakness and sensory loss in the limbs, although CSF was normal. In one case, medullar MRI was performed but was normal. One patient had Guillain-Barré syndrome (Table 3, patient 1) with a bulbar involvement. An increased protein level without pleocytosis was evident in the CSF. One patient (Table 3, patient 3) had only ocular involvement with a third right cranial nerve palsy; no lumbar puncture was done.

Eight patients (Table 4, patients 1-8) had only meningitis with pleocytosis, which was characterized by a predominance of lymphocytes in 6 cases and an increased protein level in the other 2. The glucose level was normal in all cases.

COMMENT

In this study, we report neurological manifestations that include a headache severe enough to prompt a lumbar puncture to rule out meningitis in 3.5% of hospitalized acute Q fever cases^{22,25,26,28,29,37,38} (Table 5). When we excluded patients who had only a headache and normal CSF, the prevalence of neurological symptoms in acute Q fever was 2.2%. In a review of acute Q fever in California, Clark et al²⁶ reported signs of diffuse meningeal irritation and stupor in 5% of cases (Table 5). The prevalence of neurological manifestations in acute Q fever



Bilateral periventricular edemas in a T2-weighted magnetic resonance brain image in a patient with meningoencephalitis, psychiatric symptoms, and focal deficit (aphasia).

varies considerably. Reviewing 188 cases of Q fever in Australia, Derrick³⁷ describes a single case of cerebral involvement (paresis and areflexia of the extremities) (Table 5). Reilly et al,²⁵ in a series of 103 patients with Q fever in Plymouth, England (46 acute infections, 5 chronic infections, and 52 past infections), reported an astounding 22% incidence of neurological complications in acute infections (Table 5). Clark et al²⁶ found disorientation and confusion (and occasionally encephalitic apathy) in 7% of patients. Exposure factors were rarely available in previously reported cases, but the prevalence of clinical and epidemiological conditions associated with neurological involvement and reported by our team in the retrospective analysis on acute Q fever suggests that neurological involvement in acute Q fever is not linked with predisposing conditions but with strong environmental exposure.³¹

The neurological symptoms of the 34 patients with meningoencephalitis and/or encephalitis reported herein and from the literature (Table 1 and Table 2) were non-specific. Behavioral abnormalities were common (9 patients; 26%), and Schwartz¹⁹ reported a case of manic psychosis. Furthermore, other signs of CNS involvement have been found as an extrapyramidal neurological syndrome simulating Parkinson disease (case 32²⁰), Millard-Gubler syndrome,¹⁸ cerebellar syndrome,^{6,20} and pyramidal syndrome.³⁹ A variety of neuro-ocular findings have been reported in cases of Q fever encephalitis. Shaked and Samra¹³ describe bilateral lateral rectus muscle palsy and optic neuritis with a normal CT of the head. In addition, Schuil et al¹⁵ describe bilateral optic neuritis in a farmer who presented with loss of vision in his right eye and painful eye movements; a CT scan showed bilateral optic nerve thickening. In another case, Miller Fisher syndrome was reported with bilateral paralysis of the sixth cranial nerves and with upgaze and mild bilateral ptosis¹¹; findings of a CT head scan and lumbar puncture were normal. In the 33 cases where the CSF was examined (Tables 1 and 2),⁶⁻²¹ cells were present in 23 cases (70%); cell counts ranged from 19/ μ L to 1600/ μ L. In all but 1 case, these were predominantly mononuclear cells. The glucose level was low in only 1 patient. The protein level was increased in 11. Findings of neuroradiological examinations were rarely abnormal and were not specific. Six (18%) of the 34 meningoencephalitis cases had neuroradiological abnormalities evidenced on brain imaging (Tables 1 and 2). In 1 case, there was a decreased absorption coefficient in the subcortical white matter of both hemispheres on CT scan.⁶ Magnetic resonance

Table 5. Prevalence of Neurological Involvement in the Present Study and Previous Series*

Characteristic	Present Study	Powell ²²	Derrick ³⁷	Robbins and Ragan ³⁸	Spelman ²⁸	Reilly et al ²⁵	Clark et al ²⁶	Pennington et al ²⁹
Acute Q fever	1269	72	188	380	111	46	180	41
CSF sampling	45	8	NA	3	26	7	5	10
Meningitis	8	0	0	0	2	0	1	1
(Meningo)encephalitis	17	1	1	0	0	6	9	1
Myelitis	2	0	0	0	0	0	0	0
Peripheral neuritis	1	0	0	0	0	1	2	0
Guillain-Barré syndrome	1	0	0	0	0	0	0	0

*Data are number of patients. NA indicates not available; CSF, cerebrospinal fluid.

imaging carried out in this case showed increased signal intensity on T2-weighted images in the right cerebellar hemisphere. The electroencephalogram was often abnormal (85% of cases; n=23) when this investigation was carried out (Tables 1 and 2). It showed a nonspecific involvement of the CNS.

With respect to myelitis, polyradiculoneuritis, and peripheral neuropathy, we herein report 3 cases of Guillain-Barré syndrome (Table 3), which has been reported only twice before. In 1960,²³ a 61-year-old woman had bilateral optic neuritis and sensory and motor peripheral neuropathy with paraesthesia of her legs and arms; she was treated with chloramphenicol and had no sequelae.²³ Another case of Guillain-Barré syndrome was reported in a 42-year-old woman²⁴ with facial diplegia and loss of proximal motor coordination of the lower limbs. In our study, there was 1 case of peripheral neuropathy with palsy of the third right nerve (Table 3, case 3). Among 103 cases of Q fever reported by Reilly et al,²⁵ there was 1 case of lower-limb peripheral neuropathy (wasted and flaccid) with paraesthesia in a 32-year-old man with jaundice and hepatosplenomegaly. The CSF findings were normal. There was minimal leg weakness after 1 year of follow-up. Clark et al²⁶ reported altered reflexes in 2 of 180 patients. We herein report 2 cases of myelitis (Table 3), but no cases of isolated myelitis have previously been reported in the literature (Table 5).

Severe headache associated with a meningeal syndrome is the most common neurological manifestation in Q fever.²⁶ Findings on CSF examination are usually described as normal in Q fever infection. In the present study, CSF was normal in 14 (34%) of 41 cases. We have herein reported 8 cases of aseptic meningitis (Table 4). In Spelman's study,²⁸ examination of the CSF revealed mild pleocytosis in 2 of 26 cases of lumbar puncture and an elevated protein level in 14 of the 26 cases (Table 5). In the studies of Reilly et al²⁵ and Derrick,³⁷ there was no reported case of meningitis (Table 5). In the 180-patient series reported by Clark et al,²⁶ stiffness of the back or neck severe enough to suggest meningeal irritation was observed in 9 patients (5%). Of 5 lumbar punctures performed, 1 resulted in an abnormal CSF finding. During an outbreak of Q fever among American and British troops in Italy during World War II, lumbar punctures were performed in 3 cases because of neck stiffness, but the CSF was normal in all 3 cases.³⁸ In a report of *C burnetii* occurrences in the northwest of England and North Wales between 1965 and 1967, among 10 patients with headache, neck stiffness, and pyrexia, only 1 had meningitis.²⁹ Leng-Levy et al²⁷ reported 2 cases of acute Q fever with meningitis. In total, to the best of our knowledge, 6 cases of acute Q fever with meningitis have been reported.

As for prognosis, in most instances the neurological involvement is mild. However, in the Plymouth series,²⁵ 6 of the 45 patients with acute Q fever had residual neurological impairment, including motor weakness, recurrent meningismus, blurred vision, residual paresthesia, and sensory loss involving the left leg. In our 34 encephalitis cases, recovery was complete for 22 patients within days or weeks (3 months at the most); there were no long-term relapses, and neurological sequelae were found in 7 cases (21%). There were 2 cases of peripheral neuritis with

neurological impairment. No deaths have been reported prior to this work. Recovery seems to take place regardless of treatment. Although many cases of Q fever infection will resolve without antimicrobial therapy, doxycycline (200 mg daily) is the recommended treatment. It has also been suggested, because of the possible CSF passage of *C burnetii*, that fluoroquinolones be used in cases associated with meningeal involvement because of the good CSF concentration of these compounds.⁴⁰ Other antibiotics such as erythromycin, chloramphenicol, cotrimoxazole, and ceftriaxone have been reported effective in the treatment of acute Q fever.⁴¹⁻⁴³ The type of treatment in our series does not seem to be correlated with the presence of neurological sequelae.

With respect to physiopathology, the mechanism by which infection with *C burnetii* may cause symptoms attributable to the CNS is not known. *Coxiella burnetii* has been identified by immunofluorescence in brain capillary endothelial cells,⁴⁴ and other mechanisms of injury of Q fever on CNS have been suggested such as that mediated by circulating immune complexes,⁴⁵ which are detected in acute infection. Robbins and Ragan³⁸ succeeded in isolating *C burnetii* from the CSF of 1 patient and in guinea pigs after serial passages. Our attempts to isolate *C burnetii* from CSF in 5 cases in which the CSF was abnormal were always unsuccessful. The case reported by Sawaishi et al⁶ is the first in which *C burnetii* has been isolated and detected by polymerase chain reaction in CSF. Pathological findings of the brain in a patient who died of Q fever pneumonia⁴⁶ showed small perivascular hemorrhages with capillary endothelial swelling and a few capillary thrombi. No perivascular infiltrate was noted, but Giemsa staining demonstrated coccoid and bacillary rickettsial forms inside neuroglial cells as well as extracellularly.

Our data show that individuals with specific occupational exposure are at a significantly higher risk of neurological involvement than are other patients with acute Q fever.³¹ This could mean that individuals in specific occupations are exposed to strains of *C burnetii* that have a greater pathological potential for the neurological system. Or it could mean that these individuals are exposed more frequently, and the neurological involvement results from multiple exposure and reinfection. Indeed, the clinical manifestations in these occupationally exposed individuals were different from those of others: these occupationally exposed patients had hepatitis and pneumonia less frequently and a worse prognosis even though they were not older or more frequently immunocompromised. Therefore, we consider that neurological manifestations characterize a distinct clinical entity.

In conclusion, neurological signs are prevalent in acute Q fever. Patients with CNS involvement do not demonstrate differences in predisposing conditions, but more frequently have occupational exposure to goats than patients with acute Q fever but no neurological involvement. There are 3 major neurological entities associated with Q fever: (1) meningoencephalitis or encephalitis; (2) lymphocytic meningitis (both of these entities have already been described) and (3) peripheral neuropathy (myelitis, polyradiculoneuritis, or peripheral neuritis, which have been less frequently identified). The out-

come of all 3 of these entities may be severe. Two deaths occurred in our series, and residual neurological impairment may be permanent in 4 other cases. Q fever should be included in the differential diagnosis of acute neurological disease, and serological testing should be performed in all cases of meningoencephalitis, meningitis, and peripheral neuropathy because Q fever requires specific antibiotic treatment. Moreover, systematic screening for Q fever may explain some previously undiagnosed cases of acute neurological disease.

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