CASE REPORT

Encephalopathy in an adult with cat-scratch disease

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SUMMARY

We report the case of a 53-year-old healthy man, presenting with confusion. The patient had been clinically diagnosed with cat-scratch disease (CSD) and prescribed a 10-day course of doxycycline orally. Approximately a week after he had completed the treatment, he was admitted to our department with confusion. Neurological examination revealed expressive dysphasia with no motor or sensory deficits. Cerebrospinal fluid (CSF) examination showed only increased content. Imaging with CT and MRI of the brain did not reveal any abnormalities, and funduscopy was normal. Serology confirmed *Bartonella henselae* infection. CSD-associated encephalopathy was confirmed based on the clinical manifestations, CSF findings and positive serology. The patient was treated with a combination of doxycycline and rifampin and he rapidly improved with complete neurological recovery within 7 days. Encephalopathy is an unusual manifestation of CSD in adults with excellent prognosis.

BACKGROUND

Cat-scratch disease (CSD) is a zoonotic disease, caused almost exclusively by *Bartonella henselae*. *Bartonella* spp are fastidious, facultative intracellular Gram-negative bacilli, sharing many similarities with *Brucella* spp. *B. henselae* has a worldwide distribution and the reservoir of the pathogen are domestic cats. Arthropods are the vectors of the disease, which is transmitted via their faeces or by direct inoculation. In humans, transmission occurs usually by a scratch or bite by a cat or, less frequently, after exposure to cat fleas.

Except for CSD, *B. henselae* may cause different clinical syndromes such as bacillary angiomatosis, culture-negative endocarditis and fever of unknown origin.¹ Fever of unknown origin and endocarditis can occur in both immunocompetent and immunocompromised patients. In contrast, bacillary angiomatosis occurs almost exclusively in immunocompromised patients, especially patients with advanced HIV infection with a CD4 count <200 cells/ μ L. Bacillary angiomatosis is characterised by vascular lesions that usually involve the skin and less frequently the gastrointestinal tract, lungs, lymph nodes, bone and brain while constitutional symptoms and bacteraemia may also be present. Bacillary angiomatosis is associated with significant morbidity and mortality.¹

Children account for a large percentage of CSD cases, ranging from 32.5% in a health insurance database in the USA to 79.2% in a case series from Japan; however, CSD can occur in all age groups

and it is more frequent in women (up to 62.0% of outpatients with CSD).^{2,3}

Approximately 90% of patients with CSD represent the so-called 'typical' cases, characterised by a combination of skin lesions, fever and lymphadenopathy. Skin lesions in the primary inoculation sites can be identified in 60%–90% of patients.^{4,5} These are papules or pustules presenting 3–10 days after the scratch and lasting for 1–3 weeks.

Fever is present in 60%–70% of patients and is usually below 39°C.⁴

In older CSD case series, lymphadenopathy was considered 'sine qua non' for the diagnosis of CSD.⁴ In newer case series, lymphadenopathy is not a prerequisite for CSD diagnosis; however, it is present in the large majority of cases. Usually, the lymphadenopathy is regional, involving one or more lymph nodes. The location of lymphadenopathy reflects the site of inoculation and it is more common in the upper limbs and the neck.

Less frequent manifestations, so-called 'atypical', include liver or spleen involvement and ocular manifestations (neuroretinitis, Parinaud's oculoglandular syndrome).

Neurological manifestations are uncommon and include encephalopathy, transverse myelitis, radiculitis and cerebellar ataxia.

We report a case of acute encephalopathy in an immunocompetent adult patient in order to remind this unusual manifestation of CSD.

CASE PRESENTATION

A 53-year-old healthy man suffered a cat bite on the left leg. Two days later, two reddish papules developed on the point of the bite and approximately a week later, he presented with fever with maximum temperature of 38.5°C, and left inguinal lymphadenopathy. He visited the emergency department of another hospital where the presumptive diagnosis of CSD was made and he was prescribed doxycycline tablets 100mg two times per day for 10 days. Since the clinical syndrome was typical of CSD, no serological testing for *B. henselae* was ordered at that time.

The patient completed the prescribed course of treatment, but a few days later, he presented to our emergency department with confusion. No fever, headache, vomiting or seizures were reported.

On clinical examination, the patient was alert with normal vital signs and a temperature of 36.8°C. Cranial nerve examination was normal, there were no motor or sensory deficits and deep reflexes were normal bilaterally. Gait and equilibrium were intact.

Articulation was normal; however, there was expressive dysphasia. Fluency of spontaneous

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speech was decreased, naming, repetition of spoken language, writing and reading were all impaired but comprehension of spoken language was preserved. Mini mental state examination score was 19/30. The patient had deficits in all five areas of cognitive function, that is, orientation, registration, attention and calculation, recall and language; however, there were major deficits in the attention and calculation and in the language areas.

The rest of the clinical examination was unremarkable, except for two red-brown nodules measuring approximately 5 mm each, on the lower third of the left leg and a palpable tender left inguinal lymph node, measuring 3×5 cm, with red and warm overlying skin. Funduscopy did not reveal any abnormalities.

INVESTIGATIONS

The patient was admitted to our department with a working diagnosis of Broca's aphasia. He underwent an emergent brain contrast-enhanced CT scan, which did not reveal any abnormalities. Lumbar puncture showed normal opening pressure (135 mm), no cells in the cerebrospinal fluid (CSF), CSF glucose 73 mg/dL (blood glucose was 108 mg/dL), and increased CSF protein content (655 mg/L, reference range <450). Herpes simplex virus PCR testing in CSF was negative. Brain MRI did not reveal any abnormalities.

The routine laboratory testing showed mild leucocytosis (white cell count 12.19×10^9 cells/L with 81% neutrophils) and slightly elevated C reactive protein (24 mg/L, reference range 0–5). Serum immunoglobulins were within normal range and the patient was HIV negative.

Serum *B. henselae* antibody titres were strongly positive with IgG=1:2048 (reference range ≤32) and IgM=1:160 (reference range <10).

Transoesophageal echocardiography did not reveal any heart valve abnormalities.

A CT scan showed a 3×3.5 cm heterogeneous mass on the left inguinal area, with ill-defined borders. Aspiration under CT guidance yielded pus; however, Gram staining and culture were both negative.

DIFFERENTIAL DIAGNOSIS

The diagnosis of CSD encephalopathy (CSDE) can be relatively straightforward when the typical manifestations of CSD precede the development of encephalopathy. When this is not the case, CSDE should be differentiated from other causes of acute confusion.⁶ This differential is broad and it includes infectious and non-infectious causes.

Infectious causes include other viral central nervous system (CNS) infections (most frequently herpes simplex, arbovirus and West Nile encephalitis), bacterial brain abscess, *Listeria monocytogenes* meningoencephalitis, tuberculosis, toxoplasmosis, cryptococcosis, amoebic encephalitis and spirochetal infections such as syphilis. Postinfectious encephalitis (acute disseminated encephalomyelitis) is an important consideration.⁷ In immunocompromised patients, especially with advanced HIV infection, CSDE should be differentiated by bacillary angiomatosis with CNS involvement.¹

Non-infectious causes that should be considered are cerebrovascular disease, CNS tumours, cerebral vasculitis, sarcoidosis, metabolic encephalopathies, toxic encephalopathies and medication adverse effects.

TREATMENT

The patient was diagnosed as CSD with neurological complications and he was started on a combination of oral doxycycline

100 mg two times per day and rifampin 300 mg two times per day.

OUTCOME AND FOLLOW-UP

After the third day of treatment, CNS symptoms started improving significantly, and the patient was discharged after 8 days of hospitalisation in complete neurological recovery. Because of the rapid clinical improvement, he was prescribed doxycycline and rifampin in order to complete 14 days of treatment.

In the end of treatment follow-up visit and in a second follow-up visit 1 month later, the patient was asymptomatic and had no abnormalities in neurological examination. He had returned to work and reported no difficulties in performing any of his tasks.

He was instructed to be careful with cats in the future.

DISCUSSION

Our patient presented as a typical CSD case. However, approximately 4 weeks after inoculation, he presented with global cognitive dysfunction and expressive dysphasia. Encephalopathy with or without seizures is the most common of the neurological manifestations of CSD, which also include transverse myelitis, radiculitis and cerebellar ataxia.⁸

The information regarding the frequency of CSDE is conflicting. In one of the largest case series, Carrithers *et al* reported that only 3/1200 (0.25%) of their patients presented with CSDE but based on unpublished information, they assumed that CSDE was more frequent than reported. They hypothesised that CSDE was as frequent as the encephalitis caused by measles, mumps, chickenpox or rubella.⁴ On the other hand, Murakami *et al* reported CSDE in 4/130 (3.1%) patients, while Ghandi *et al* state that CSDE 'probably occurs in 2% to 4% of all CSD cases recognised, although estimates range as widely as 1% to 7%'.¹

It is not clear which age group is more frequently affected. Carrithers *et al*, in a series which included 76 CSDE cases, reported that it was more common in younger patients.⁹ Others however have reported that CSDE is more frequent in patients >60 years old (3.8% vs 0.6%, OR 6.3).¹⁰ In most case series of CSD, there are no data on the frequency of CSDE in immunocompromised patients.^{2,3}

The interval between the onset of CSD and the development of encephalopathy ranges from a few days to 2 months.^{9,11} It is important to note that previous treatment for CSD does not preclude encephalopathy.¹² A minority of patients develop CSDE without the typical manifestations of CSD. Approximately 50% of patients have no or low-grade fever.⁹

Patients with encephalopathy usually present with confusion and disorientation that may be accompanied with depressed level of consciousness, ranging from lethargy to coma. Seizures occur in approximately half of the patients and range from localised, self-limited clonic seizures to status epilepticus.^{9,13} Combative behaviour, mostly in children, is considered a characteristic manifestation of CSDE.⁹ Focal neurological signs occur in a minority of patients and include aphasia, hemiparesis cranial nerve palsy and ataxia.⁸

The diagnosis of CSD in our patient was based on the typical clinical manifestations. Encephalopathy was attributed to CSD, as it followed CSD in the expected time frame, the serology for *B. henselae* was consistent with acute infection and other possible causes of encephalopathy had been excluded. The diagnosis of CSDE is straightforward when CSDE occurs during the course of an already diagnosed case of CSD, as it was in our patient.

In the uncommon patient in which the typical manifestations of CSD are lacking, diagnosis can be established by excluding other causes of encephalopathy and serologically confirming CSD. There are no specific imaging or laboratory findings for CSD. In the majority of patients, CT and MRI are normal. There are minor and non-specific abnormalities in the CSF, including mild lymphocytosis (usually <50 cells/ μ L, 70%–100% lymphocytes) in 30% of patients and elevated protein (up to 930 mg/L) in 35% of patients. Electroencephalogram is abnormal in 80% of patients, showing background slowing consistent with encephalopathy.⁹

We have no detailed data regarding serology for *B. henselae* in patients with CSD, as the largest case series on CSD have been published before the serological test was introduced. Dyadencho *et al* confirmed the diagnosis of CSD by using PCR to identify *B. henselae* DNA in both the lymph node and the CSF of their patient.¹⁴ Molecular techniques for *B. henselae* DNA detection might prove useful diagnostic tools in the future.

The clinical course of the patient was uneventful and he recovered completely. The prognosis of CSD is excellent. The vast majority of patients recover in a matter of days to weeks, although residual neurological defects may remain in the occasional patient.⁹ The role of antibiotics for CSD in immunocompetent patients is not clear. In cases of encephalopathy, if treatment is to be given, the combination of doxycycline 100 mg two times per day and rifampin 300 mg two times per day should be preferred.¹⁵ In contrast, immunocompromised patients with *B. henselae* infection can have serious or fatal manifestations

such as bacillary angiomatosis or disseminated disease; therefore, they should always be treated with antibiotics. Depending on the localisation of the lesions, doxycycline 100 mg two times per day in combination with rifampin 300 mg two times per day or gentamicin (1 mg/kg intravenously every 8 hours) is used.^{1 15}

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REFERENCES

- Gandhi TNS, Welch LN, Koehler DF, *et al*. Bartonella, Including Cat-Scratch Disease. In: Bennet JED, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th edn. Philadelphia: Saunders, 2015:2649–63.
- Nelson CA, Saha S, Mead PS. Cat-Scratch Disease in the United States, 2005–2013. *Emerg Infect Dis* 2016;22:1741–6.
- Murakami K, Tsukahara M, Tsunooka H, *et al*. Cat scratch disease: analysis of 130 seropositive cases. *J Infect Chemother* 2002;8:349–52.
- Carithers HA. Cat-scratch disease. An overview based on a study of 1,200 patients. *Am J Dis Child* 1985;139:1124–33.
- Margileth AM. Cat-scratch disease update. *Am J Dis Child* 1984;138:711–3.
- Delirium and Other Confusional States. In: Ropper AH, Samuels MH, Klein JP, eds. *Adams and Victor's Principles of Neurology*. 10th edn. New York: McGraw-Hill, 2014:421–33.
- Gluckman SJ. Viral encephalitis in adults. Post TW, ed. Waltham: UpToDate, 2018.
- Marra CM. Neurologic complications of Bartonella henselae infection. *Curr Opin Neurol* 1995;8:164–9.
- Carithers HA, Margileth AM, disease C-scratch. Acute encephalopathy and other neurologic manifestations. *Am J Dis Child* 1991;145:98–101.
- Ben-Ami R, Ephros M, Avidor B, *et al*. Cat-scratch disease in elderly patients. *Clin Infect Dis* 2005;41:969–74.
- Lyon LW. Neurologic manifestations of cat-scratch disease. Report of a case and review of the literature. *Arch Neurol* 1971;25:23–7.
- Centers for Disease Control and Prevention (CDC). Encephalitis associated with cat scratch disease--Broward and Palm Beach Counties, Florida, 1994. *MMWR Morb Mortal Wkly Rep* 1994;43:915–6.
- Laswell EM, Chambers KD, Whitsel DR, *et al*. New-onset refractory status epilepticus in an adult with an atypical presentation of cat-scratch disease: successful treatment with high-dose corticosteroids. *Pharmacotherapy* 2015;35:e106–10.
- Dyachenko P, Ziv M, Raz R, *et al*. Cat scratch disease encephalopathy in an immunocompetent patient. *Eur J Intern Med* 2005;16:610–1.
- Rolain JM, Brouqui P, Koehler JE, *et al*. Recommendations for treatment of human infections caused by Bartonella species. *Antimicrob Agents Chemother* 2004;48:1921–33.

Learning points

- Cat-scratch disease (CSD) can rarely be complicated with central nervous system (CNS) involvement in the form of encephalopathy, myelitis or focal signs such as expressive dysphasia.
- The diagnosis is based on the preceding CSD clinical syndrome, positive serology for *Bartonella henselae* and exclusion of other causes of encephalopathy.
- The recommended treatment is the combination of doxycycline 100 mg two times per day orally and rifampin 600 mg daily orally for up to 4–6 weeks.
- The prognosis of CNS involvement in CSD in immunocompetent patients is excellent, with most patients recovering fast and completely.

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