CASE REPORT

Cat Scratch Disease-associated Encephalitis Followed by Parkinsonism

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Abstract:
Cat scratch disease (CSD) is a zoonotic infection caused by Bartonella henselae typically resulting in self-limited regional lymphadenopathy. Encephalitis is a complication with a supposedly benign prognosis, but we encountered an exceptional case. A 19-year-old Japanese woman presented with status epilepticus. She was diagnosed with CSD-associated encephalitis based on her history of contact with a kitten and a high titre of serum IgG to B. henselae. Multimodal treatment ameliorated her encephalitis, but neurological sequelae including spastic paraparesis, persisted. After several months, she developed age-disproportionate parkinsonism inconsistent with a neurodegenerative disease. In conclusion, CSD-associated encephalitis can result in severe neurological sequelae and post-encephalitic parkinsonism.

Key words: Bartonella henselae, cat scratch disease-associated encephalitis, post-encephalitic parkinsonism, nigrostriatal degeneration, dopamine transporter single-photon emission computed tomography, neuromelanin-related magnetic resonance imaging

Introduction

Cat scratch disease (CSD) is a zoonotic infection caused by the Gram-negative bacillus Bartonella henselae. This agent is transmitted to humans by a scratch or bite from reservoir cats harbouring it (1). Although CSD is clinically characterized by self-limited regional lymphadenopathy with skin eruption and a low-grade fever, up to 2% of cases develop neurological involvement, typically in the form of encephalitis with a fever, headache, decreased arousal, and epilepsy (1-3). It is difficult to diagnose this type of encephalitis due to the lack of specific symptoms and examination findings (4-6). The natural clinical course of CSD is reportedly benign, whereby most patients completely recover, irrespective of typical lymphadenopathy or extranodal involvement, including encephalitis (1-3).

We herein report a rare case of CSD-associated encephalitis with neurologic sequelae that later progressed to age-disproportionate parkinsonism.

Case Report

A 19-year-old Japanese woman was transferred to a hospital due to generalized convulsions following a fever and headache. Her consciousness was disturbed, showing no signs of eye opening during pain stimulation. Hyperreflexia and pathological reflexes were observed in both her extremities. Neither skin eruptions nor signs of lymphadenopathy were observed. She had no remarkable medical history. Blood tests showed a slight increase in C-reactive protein levels (2.49 mg/dL). In her cerebrospinal fluid (CSF), protein concentrations were mildly elevated (64 mg/dL), while the cell count was normal (<1/μL). No abnormality was found on a brain magnetic resonance imaging (MRI), although an electroencephalogram (EEG) depicted signs of suppression and burst.

Phenytoin and phenobarbital were immediately adminis-

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tered. Treatment with acyclovir and ceftriaxone was empirically initiated as encephalitis, followed by prednisolone pulse therapy. Three days after admission, convulsions were increased, and continuous intravenous infusion of propofol and thiopental was initiated on mechanical ventilation. Serum autoantibodies were negative, including antinuclear, anti-double strand DNA, anti-beta2-glycoprotein 1, anti-Smith, anti-ribonucleoprotein, anti-Sjögren’s syndrome related antigen A and B, and anti-neutrophil cytoplasmic antibodies. In CSF studies, culture, polymerase chain reaction (PCR) of herpes-simpex, and antibodies to cytomegalovirus and Epstein-Barr virus were all negative; however, remarkably high concentrations of interleukin-6 (IL-6; 72.5 pg/mL) and IgG (9.6 mg/dL) were detected.

Although her condition could have been categorized as encephalopathy with an emphasis on defective pleocytosis, the increased IgG production accompanied by abundant IL-6 in the central nervous system strengthened the probability of encephalitis according to a case definition by the International Encephalitis Consortium (7). Importantly, it was revealed that she had been bitten by a kitten several days before the onset. Therefore, the administration of minocycline was initiated according to the diagnosis of CSD three weeks after admission, leading to a gradual resolution of her status. Therefore, the administration of minocycline was initiated according to the diagnosis of CSD three weeks after admission, leading to a gradual resolution of her status epilepticus and consciousness (1). An indirect immunofluorescence assay (IFA) with serum showed a significantly high titre of IgG to B. henselae (1:256); this encephalitis was considered to be associated with CSD. One month after this examination, we confirmed a remarkable decrease of the serum IgG titre (1:64). PCR of her CSF failed to detect the sequence of B. henselae.

After two-month multimodal treatment, her encephalitis was resolved, and her alertness fully recovered, although mild cognitive dysfunction, spastic paraparesis, and symptomatic epilepsy remained as sequelae. Repeated brain MRI only showed diffuse but slight cerebral atrophy without any focal brain lesions. No intra- or extramedullary lesions of the cervical or thoracic cord were detected by MRI. Although spastic paraparesis was potently induced by inflammation of the bilateral pyramidal tracts, it was difficult to conclude its cause.

During her half-year rehabilitation, she regained the ability to walk with a cane and was discharged home. After that, she attended a psychiatry clinic, not a neurology clinic, to control her epilepsy. However, she visited a neurology clinic once for a low-grade fever and headache with slight throat discomfort 10 months after remission of encephalitis. Repeated brain MRI showed no abnormalities, except for post-encephalitic cerebral atrophy. However, lumbar puncture revealed an elevated IgG index (1.10) without an increase in cells or proteins in the CSF.

The common cold-like symptoms disappeared with the administration of antibiotics for a few days, leaving the pathological significance elusive. However, she experienced mild progression of gait disturbance and bradykinesia around that time. Despite noticing her bradykinesia and slight hand tremor, her parents considered these symptoms to be derived from her depressive mood related to the encephalitic sequelae. The attending physician at the psychiatry clinic had not highlighted her changing motor complications, as these symptoms appeared to be masked by persistent spastic paraparesis. The progression of her subjective symptoms eventually became obscure, so she had no chance to consult with neurologists.

However, she eventually visited a neurology clinic again at 38 years old with a complaint of deteriorated gait disturbance due to suspension of ambulatory rehabilitation during the coronavirus disease 2019 pandemic. She exhibited an expressionless face and a monotonous and slow speech. On the upper extremities, left-dominant mild rigidity was detected without paresis, hyperreflexia, or pathological reflexes. The left-dominant rigospecticism was found on the lower extremities, accompanied by bilateral hyperreflexia and Babinski sign. Superficial and deep sensations were almost normal on the extremities and trunk. A slight kinetic tremor, not dysmetria, on the upper extremities emerged in a finger-to-nose test, which was also left-dominant. Bradykinesia was clear when she stood up from sitting in a chair. She showed truncal instability, requiring a handhold to keep standing. Her gait was characteristically spastic and shuffling, with left lower extremity deceleration, and she required Lofstrand crutches to stabilize her gait. The rigidity and kinetic tremor on the upper extremities and bradykinesia, accompanied by her expressionless face and monotonous speech, represented parkinsonism. The rigidospecticism of the lower extremities could be interpreted as an addition of the rigidity to the persistent spastic paraparesis. The left-dominance of her rigidity, kinetic tremor, and rigidospecticism were consistent with the occurrence of identical parkinsonism in the upper and lower extremities. Hyperreflexia and Babinski sign on the lower extremities were accompanying signs of the spastic paraparesis.

Although clobazam and zonisamide were efficaciously prescribed for epilepsy, there were no medical records of any parkinsonism-inducing drugs having been administered. No family history of Parkinson’s disease or related disorders was found. Typical non-motor symptoms of Parkinson’s disease, such as autonomic failure and rapid eye movement sleep behaviour disorder, were not observed. Brain MRI showed mild atrophy of the frontal and temporal lobes as a post-encephalitic change without any causative findings (Figure A). However, neuromelanin-related MRI detected a mild deficit of neuromelanin in the bilateral substantia nigra pars compacta (SNpc) (Figure B). Consistently, 123I-ioflupane dopamine transporter single-photon emission computed tomography (DAT-SPECT) revealed a mild decrease in the presynaptic dopamine uptake, while the uptake pattern remained morphologically normal (Figure C). These findings indicated post-encephalitic parkinsonism rather than a primary neurodegenerative disease.
She exhibited mild cognitive dysfunction in processing speed in the Visual Cancellation Task (52 s >33.9±5.7 s) and Symbol Digit Modalities Test (41.8% <64.7%±7.3%) of the Clinical Assessment for Attention and the Japanese version of the Trail Making Test (TMT-A, 42 s; mean+1SD, 37 s, mean+2SD, 45 s; TMT-B, 64 s; mean+1SD, 55 s, mean+2 SD, 65 s), developed by The Japan Society for Higher Brain Dysfunction. These cognitive test results suggested a decreased function of the frontal lobe.

A low-dose (200 mg/day) levodopa/decarboxylase inhibitor (L-Dopa/DCI) was administered, and her parkinsonism was partially relieved. After rehabilitation during hospitalization for one month, she was able to walk with a T-cane. Intriguingly, her processing speed also improved to a normal range (TMT-A, 32 s; TMT-B, 36 s). Several months after the initiation of L-Dopa/DCI, she maintained her condition without developing parkinsonism or bradyphrenia.

### Discussion

Surprisingly, most patients with CSD-associated encephalitis reportedly recover without any neurological sequelae (2, 3). Rare descriptions of specifying *B. henselae* in the CSF may affect the mechanistic hypothesis of this encephalitis (1, 4-6). A host immune response, which probably represents para-infectious autoinflammation, has been believed to underlie this encephalitis. Given the usual lack of pleocytosis, toxic encephalopathy has been another assumption (1). However, we found an autopsy case characterized by direct brain invasion of *B. henselae*, as demonstrated through positive results by PCR and Southern blotting of brain tissue (8). Another autopsy case failed to detect *B. henselae* in the CSF or brain tissue, although the microglial nodules associated with lymphocytic infiltration and damage to neurons in the brain parenchyma pointed to the direct invasion of the concerned organism (9). These dissociated observations suggest that the mechanisms underlying CSD-
associated encephalitis might be divided into direct brain infection with a poor prognosis and para-infectious processes with clinical recovery.

Our patient was serologically diagnosed with CSD-associated encephalitis based on a high titre of serum IgG to *B. henselae* (titre of 256) and its 4-fold decrease (titre of 64), both of which were detected by an IFA. It has been demonstrated that a serum titre of ≥64, accompanied by a ≥4-fold change, has diagnostic value (10). However, the results of CSF PCR for *B. henselae* were negative. Considering the high concentrations of IL-6 and IgG in the CSF, a para-infectious autoimmune encephalitis is the most likely aetiology. Although minocycline, a tetracycline recommended for the treatment of systemic CSD, was administered for encephalitis of our patient, direct brain infection of *B. henselae* could not be supported based on her clinical recovery with multimodal therapy (1). Despite the lack of evidence supporting direct infection, severe neurological sequelae (cognitive dysfunction, spastic paraparesis, and symptomatic epilepsy) unexpectedly remained. This suggests that CSD-associated encephalitis is not always a benign disease. The limited information available concerning such encephalitis might lead to bias in the disease concept.

Parkinsonism following CSD-associated encephalitis, as was observed in our patient, is rare. Neuromelanin-related MRI and DAT-SPECT scans indicated that a loss of dopaminergic neurons at the SNpc induced parkinsonism in our patient. This suggests that hypoxic encephalopathy with status epilepticus might not underlie her parkinsonism, since hypoxia in the brain preferentially damages the postsynaptic dopaminergic neurons at the SNpc, resulting in post-synaptic dopaminergic neurons (11-13). In addition, she exhibited no lesions of pallidus globus, caudate nucleus, or putamen on brain MRI, which are typically detected in patients with parkinsonism induced by hypoxic encephalopathy (13-16).

However, while nigrostriatal dopaminergic damage is critical to the development of Parkinson’s disease (17), the pathogenesis of our patient’s parkinsonism might not be identical to that of Parkinson’s disease. This is an atypical case of Parkinson’s disease, presenting with a young onset of sporadic parkinsonism without any typical non-motor symptoms. There was no remarkable efficacy of L-Dopa/DCI on her rigidity and bradykinesia (17). Furthermore, the lack of any morphological changes in the dopaminergic uptake at the striatum, known as “egg-shaped” and “eagle-wing” patterns, on DAT-SPECT meant that this case was unlikely to be one of Parkinson’s disease (18). Intriguingly, several bacteria, such as *Helicobacter pylori* and *Mycobacterium tuberculosis*, which usually infect regions outside the brain, may result in parkinsonism (19). Locally produced cytokines and lipopolysaccharides (LPS) have been shown to cross the blood-brain barrier into the brain parenchyma and activate resident microglia, leading to the degeneration of nigrostriatal dopaminergic neurons by expanding inflammation while producing neurotoxic substances (e.g. reactive oxygen and nitrogen species) and inducing metabolic imbalance (20). In the context of encephalitis, this dopaminergic damage is easily induced by the unnecessary hematogenous transport of cytokines and LPS to the brain. Notably, our patient showed abundant production of IL-6 in the CSF, which can reflect fulminant brain inflammation and severe damage to dopaminergic neurons. Enhanced IgG production in the CSF following remission of acute encephalitis pointed to the possibility of prolonged brain inflammation through the positive feedback loops linked to microglial activation (21). Accordingly, acute encephalitis followed by smoldering inflammation might have induced the degeneration of dopaminergic neurons at the SNpc, resulting in post-encephalitic parkinsonism. Given that her parkinsonism and abnormality at the DAT-SPECT remained mild, the smoldering phase may have been limited to the short term. Importantly, the modest efficacy of L-Dopa/DCI on the parkinsonism of our patient implies the encephalitic involvement of the postsynaptic dopaminergic system in the striatum as well as the nigrostriatal pathway, although the lack of MRI lesions at the basal ganglia indicated that the postsynaptic damage is not severe.

We unexpectedly detected the mild improvement of her processing speed in TMT after administration of L-Dopa/DCI. As discussed above, our patient had impairment of the nigrostriatal pathway, which may induce the functional disability observed in patients with Parkinson’s disease (17). In Parkinson’s disease, cognitive dysfunction is associated with a decreased dopaminergic input to the caudate nucleus (22), and the frontal lobe dysfunction, including thinking time as well as the working memory, is potently improved by L-Dopa-replacement therapy (23, 24). Therefore, the improvement of the processing speed in our patient suggested that the basal ganglia dysfunction induced by the CSD-associated encephalitis might have been partially reversed by recruitment of dopamine. The improvement of the motor function may have improved the patient’s performance in TMT, given that cognitive processing and motor control are connected to a wide range of neural systems (25). However, it has been demonstrated that cognitive slowing can originate from the striatum or premotor cortex, which are independent of the brain regions related to motor slowing, in patients with Parkinson’s disease (26).

To our knowledge, there has only been one case report of parkinsonism induced by CSD-associated encephalitis (27). The reported patient shares several clinical features with ours: 1) she was a 16-year-old young woman, 2) she required mechanical ventilation due to status epilepticus, 3) conventional MRI failed to detect any brain lesions, and 4) she was serologically diagnosed but lacked CSF PCR data. However, these are common features in patients with CSD, since it has been clarified that CSD generally occurs in children and adolescents, and CSD-associated encephalitis reliably induces epilepsy and rarely shows MRI brain lesions or positive PCR results of *B. henselae* (1, 4-6). As discussed above, the lack of detection of infectious agents in the CSF...
implies autoinflammatory encephalitis rather than direct brain infection. However, the parkinsonism in the previously reported patient differed markedly from that in our own patient in the following points: 1) oral dyskinesia and upper-limb dystonia simultaneously emerged with parkinsonism, 2) these integral movement symptoms were detected during the acute (not remission) phase of encephalitis, 3) antibiotics (not L-Dopa/DCI) were effective in ameliorating her parkinsonism, 4) parkinsonism disappeared soon after the remission of encephalitis, and 5) a decrease in postsynaptic dopamine D2 receptors (not presynaptic dopamine transporters) was noted on 123I-iodobenzamide SPECT. These differences in the symptoms, onset time, main lesion, and prognosis indicate that the mechanisms underlying parkinsonism for these two patients lie on a spectrum of autoinflammatory encephalitis. Although precise distinctions are elusive here, we notably found that parkinsonism could emerge several months after remission of acute CSD-associated encephalitis.

Encephalitis lethargica is a prototypic cause of post-encephalitic parkinsonism that was epidemic from 1916 to the 1930s around the world (28). Although the aetiology was classically assumed to be toxicosis and viral infection, autoimmunity has been recently proposed based on the detection of antibodies against the basal ganglia antigens, including the dopamine D2 receptor (29, 30). According to the clinical presentation during the acute phase, this encephalitis is classified into somnolent-ophthalmoplegic, hyperkinetic, or amyostatic-akinetic forms (28). Parkinsonism is detected immediately or decades after acute encephalitis, characterized by bradykinesia and rigidity preferentially on the upper limbs and is often accompanied by various involuntary movements and psychiatric manifestations (28). Our patient presumably developed bradykinesia and rigidity-predominant parkinsonism several months after the amelioration of acute encephalitis, which was influenced by other encephalitic complications. These clinical features may be conceivable as indicative of post-encephalitic parkinsonism, although the acute encephalitis in our patient could not be categorized as encephalitis lethargica. The brain imaging data of patients with encephalitis lethargica have not been organized due to the obscure definition of symptoms, heterogenous underlying aetiology, and a lack of MRI and DAT-SPECT being performed during the epidemic (28, 31). In pathological studies of brains from patients with encephalitis lethargica, the loss of neurons is most prominent at the substantia nigra among affected brain sites, including the basal ganglia, thalamus, pons, and medulla (28, 31). Therefore, the impaired nigrostriatal pathway depicted in our patient with neuromelanin-related MRI and DAT-SPECT may be consistent with post-encephalitic parkinsonism. However, in a study of aseptic encephalitis inducing movement disorders, 53 of 67 patients with post-encephalitic parkinsonism had brain lesions on MRI, most of which were located on the bilateral thalamus, putamen, caudate, and substantia nigra (32). Despite the highly frequent brain lesions, post-encephalitic parkinsonism has been demonstrated to spontaneously cease and improve with or without L-Dopa-replacement therapy (32). Intriguingly, the selective involvement of the substantia nigra on MRI appears to reflect particularly good recovery (33, 34). Therefore, the defective brain lesions on conventional MRI in our patient were not typical of post-encephalitic parkinsonism but may have been specific for parkinsonism induced by CSD-associated encephalitis (1, 27). The mildness of our patient’s parkinsonism may reflect a common pathophysiology with previously reported cases of post-encephalitic parkinsonism.

We encountered a young woman with CSD-associated encephalitis with neurological sequelae, which has been historically described as rare. Most strikingly, this patient developed age-disproportionate parkinsonism in the remission phase of acute encephalitis. This clinical manifestation indicates that CSD-associated encephalitis does not always follow a benign course and that post-encephalitic parkinsonism may be induced by CSD-associated encephalitis.

The patient and her parents provided their written informed consent. The study was approved by the Ethics Committee of Hokkaido Neurosurgical Memorial Hospital.

The authors state that they have no Conflict of Interest (COI).

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