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Epilepsia partialis continua in cat scratch disease

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Cat scratch disease (CSD) is a world-wide, diffuse, non-epidemic infection caused by the Gram-negative bacillus *Bartonella henselae*. The occurrence of encephalopathy represents an infrequent and atypical complication, whose manifestations include ischemic strokes, transverse myelitis and epileptic seizures. Status epilepticus has been described as the most frequent emergency in CSD encephalopathy. In this report, we describe a case of CSD complicated by an epilepsia partialis continua (EPC) manifested as rhythmic movements of the flexor muscles of the left hand. Although CSD is a benign, self-limited disease and a complete neurological recovery usually occurs, in the present case the EPC resulted in a partial epilepsy. Magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT) and back-averaged EEG data recorded during myoclonic activity document this CSD complication.

Key words: cat scratch disease (CSD); epilepsia partialis continua (EPC); SPECT; MRI; EEG back-averaging.

INTRODUCTION

Cat scratch disease (CSD) is a relatively common cause of local, benign and self-limited lymph node alteration[1], seldom associated with involvement of the central nervous system (CNS)[2]. *Bartonella henselae*, a Gram-negative bacillus, is the aetiologic agent of the disease[3,4]. Usually benign, it may induce encephalopathy and seizures, either manifested as isolated attacks or status epilepticus[5–7].

Although CSD-induced encephalopathy is an infrequent manifestation and several hypotheses have been suggested as possible pathogenetic factors of the neural damage, the aetiopathogenesis of this complication remains unclear.

In this study, we describe a case of CSD encephalopathy characterised by an unusual manifestation of epilepsia partialis continua (EPC), followed by residual partial epilepsy.

SUBJECT AND METHODS

Six weeks after being scratched on the hands by a pet kitten, a 17-year-old female living in suburban South Sardinia (Italy), developed an acute, progressive frontal headache, followed by several episodes of tonic convulsions and a state of disorientation and confusion lasting 2 hours. An examination of her previous medical records provided no remarkable findings.

Neurological examination and blood samples, performed soon after the patient's admission to hospital, yielded a sedimentation rate of 35 mm/hour, a WBC count of 17 000 with a left shift, and a body temperature of 38 °C. A lumbar puncture yielded clear, cell-free cerebral spinal fluid (CSF) with a normal protein content, negative for oligoclonal bands. The search for a possible autoimmune genesis with the study of anti-nuclear antibodies, anticardiolipine, anti-neutrophil cytoplasmic antibodies (ANCAs) tested for c-ANCAs and P-ANCAs, IgG and IgM, ENA screening, and the test for lupus-like anticoagulant (DRVVT and DRVVT miscela ratio) yielded normal results. Moreover, since CSD may complicate acquired immunodeficiency diseases, the subject was tested for the antibodies HIV 1, 2 (ELISA: not reactive) and for CD4/CD8 (ratio 1.08). In order to rule out other possible causes of encephalitis, the TORCH test was also performed (ELISA: antibodies absent). An EEG recorded 2 hours after admission showed diffuse

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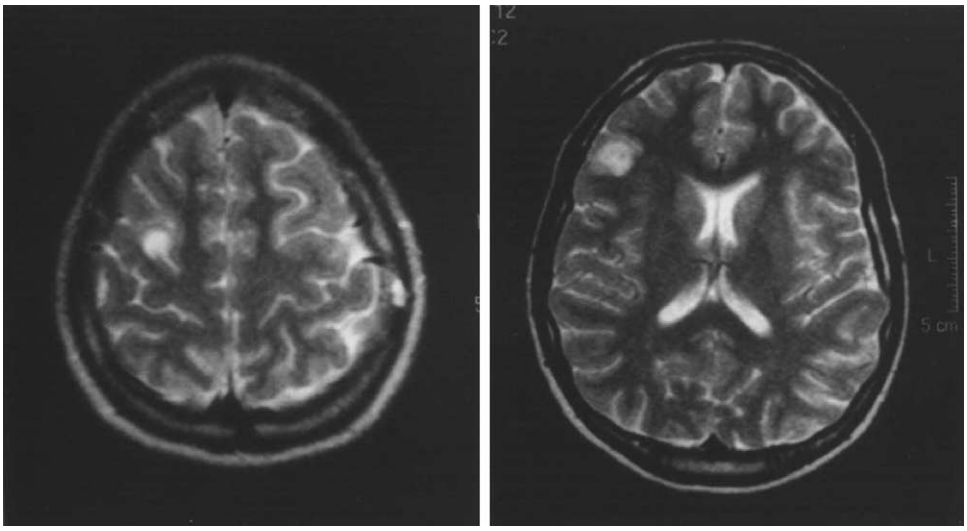

Fig. 1: T2-weighted brain MRI reveals two large, well-defined areas of an increased bright signal without mass effect within the right frontal cortex.

slow activity that was larger in the frontal–parietal right leads. A brain magnetic resonance imaging (MRI) performed at the same time showed cortical and subcortical lesions on the right hemisphere that failed to show contrast enhancement after gadolinium (Fig. 1). Antiepileptic treatment with Carbamazepine (CBZ) was started at the dose of 600 mg/day. After the first episodes of seizures, the patient showed six episodes of myoclonic movements during the following 48 hours, which were localised to the flexor digitorum of the left hand and lasted from 4 to 15 seconds and occurred without alteration of the status of consciousness. Four days after admission, the patient manifested an episode of EPC characterised by rhythmic myoclonic movements of the flexor digitorum of the left hand (2–4 cycles/second). This episode was reported to the medical staff by the patient 15 minutes after its onset. The patient's status of consciousness was apparently normal, but when she was asked about her feelings after the episode, she described a 'sensation of extraneity without fear' as if the episode 'occurred to another person'. This manifestation lasted 37 minutes. Under polygraphic video-EEG recording (Brain Quick System 98, Micromed, Mogliano Veneto, Italy), the patient was treated with an i.v. bolus of 10 mg Clonazepam, which was followed by a complete remission of the clonic movements and a suppression of the spiking activity with persistence of the slow waves. The polygraphic EEG tracings were subsequently back-averaged off-line.

The EMG obtained from the left flexor digitorum was evaluated with respect to the EEG activity of the corresponding sensory-motor area recorded at the right temporal–parietal leads. This analysis showed a concordance between the movements of the second and third finger of the left arm and the spikes recorded at the right temporal–parietal leads (Fig. 2). Moreover, visual, acoustic and sensory evoked potentials (VEPs, BAEPs and SSEPs), yielded normal results. A single photon emission computed tomography (SPECT) performed during the interictal phase after the first seizure episode with 740 MBq of ^{99m}Tc-ethyl cysteine dimer (ECD) showed several areas of cortical and subcortical hypoperfusion localised in the right cortex (Fig. 3). Five days after admission the patient manifested a cutaneous rash and an axillary and cervical lymphadenopathy. As the patient was treated with CBZ, this manifestation was considered a side effect of this treatment. The CBZ was discontinued and the treatment was shifted to 600 mg/day of valproic acid (VA).

Since the patient's temperature persisted at 38.5 °C, the anamnestic observation of a cat scratch associated with transitory lymphadenopathy, attributed '*prima facie*' to CBZ treatment, suggested the rationale of a test for CSD. Indirect fluorescent antibody testing for CSD revealed *B. henselae* serology positive at a titre of 1:186 (cut-off: 1:58) 10 days after the onset of the symptoms. This positivity prompted a CSF PCR analysis in the attempt to establish *B. henselae* as the specific cause of the seizure disorder, but the results were negative. Tests for mononucleosis, Group A *Streptococcus*, syphilis, tuberculosis and brucellosis, were negative. Tests for 'Tularaemia' were not performed as this disease has never been described in Sardinia and, although not infrequent in Central Europe, it is rare in all South Mediterranean countries.

Though there is no general agreement on the efficacy of the antibiotic treatment in CSD, the unusual severity of the symptomatology urged us to treat the subject

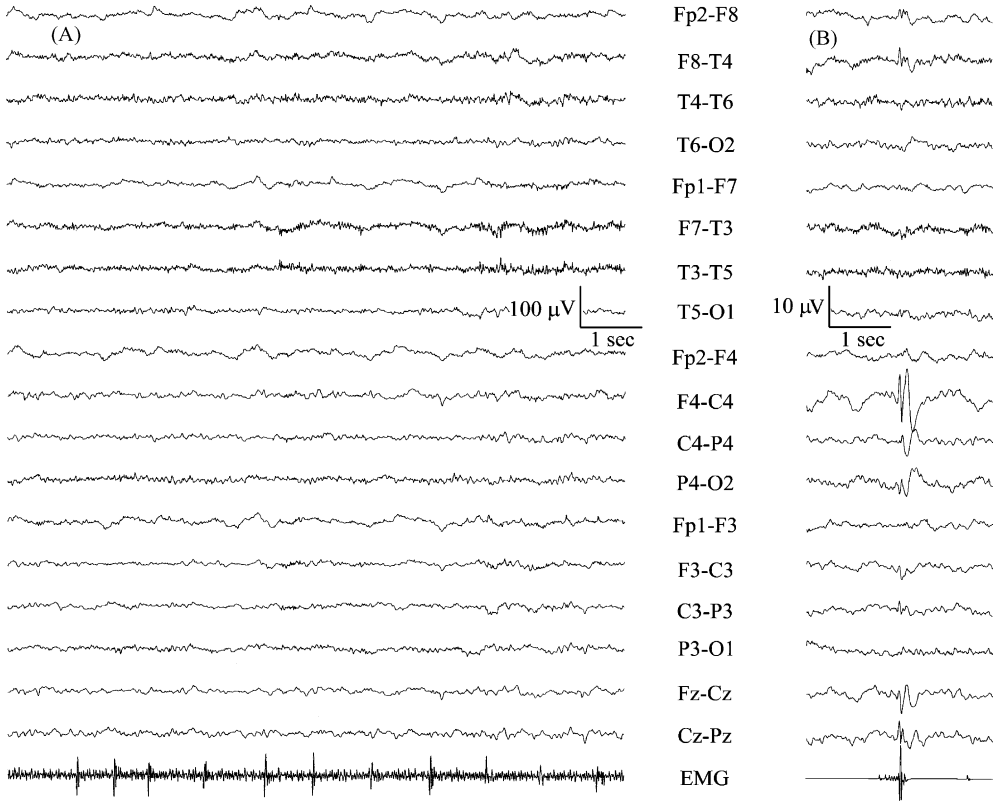

Fig. 2: EEG and back-averaging. Left: Desynchronised activity mixed with diffused theta waves. The EMG shows bursts of myoclonic activity in the muscle proper flexor of the third finger. Right: Back-averaging of 300 events shows the coherence between myoclonus and right frontal–parietal spikes.

with Amoxicilline at a dose of 3 g/day. This therapy, which was maintained for 1 week, was followed by a dose of 1.5 g/day for 2 weeks. Though complete regression of the temperature was observed within 4 days after antibiotic administration, myoclonic movements were sporadically observed. In particular, this abnormal motor pattern, strictly localised to the second and third finger of the left hand, lasted 1–3 to 5–8 seconds, and was reported by the patient and her family members, who witnessed attacks with one to four episodes a day. Despite the fact that VA was increased to 1200 mg/day for the optimal serum range of 83 μg/ml, isolated myoclonic jerks were observed for 5 weeks. The serum titre for *Bartonella*, which was repeated after 2 months, returned to 1:86.

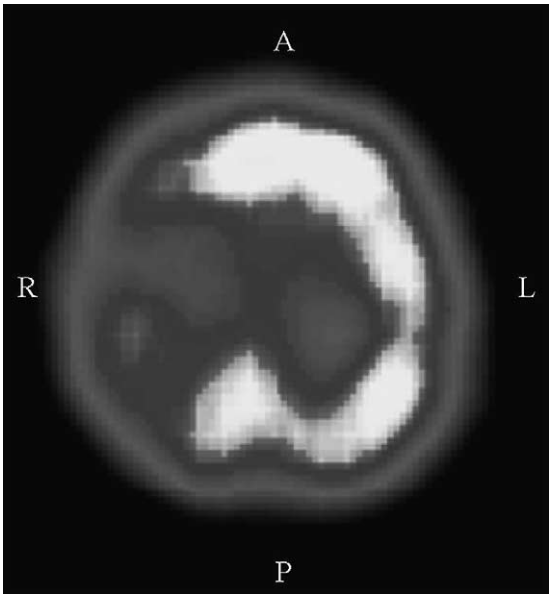

Fig. 3: ^{99m}Tc-ECD cerebral SPECT shows frontal, parietal and temporal cortical right hypoperfusion.

MRI controls were scheduled weekly during 2 months. Three weeks after the first examination, MRI showed an almost complete regression of the cortical and subcortical lesions, while new small alterations similar to those described initially were observed (not shown). This finding and the occasional myoclonic movements of the second and third finger of the left hand contrasted with the normal neurological and psychological conditions of the subject. Clinical normalisation was assessed with a further MRI at the end of the second month, which yielded a completely normalised finding. The patient was discharged 10 weeks after admission and the antiepileptic treatment was monitored. A new MRI and a SPECT performed after 2 more months confirmed the absence of cere-

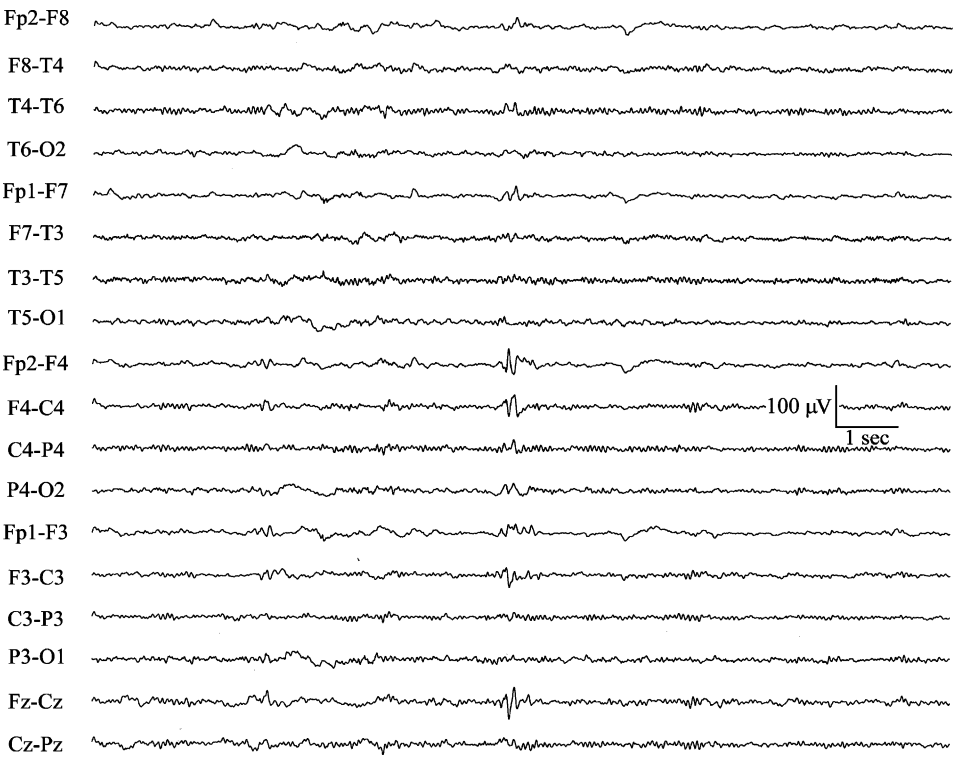

Fig. 4: EEG after 24 months of 8–12 Hz low-voltage irregular activity mixed with rare spikes localised over the right frontal–parietal leads.

bral alterations. The patient was monitored with EEG recordings every 2 months. Despite the clinical remission, the EEG showed rare low-voltage spiking activity localised in the right parietal–temporal leads.

Fourteen months after the first episode, the patient experienced a feeling of 'sudden confusion' lasting about 1 minute. A new EEG showed medium-voltage temporal–parietal spiking activity (Fig. 4) and consequently the diagnosis of secondary partial epilepsy was considered. VA was reduced (300 mg/day) and lamotrigine (LMT) was added at the dose of 50 mg/day. After a slow increase (steps of 50 mg every 10 days), the optimal dose of LMT for seizure control was established at 300 mg/day and VA was discontinued. Though LMT proved efficient in preventing further seizures, the EEG follow-up, including the last record 2 years after the episode, documented a right frontal–temporal–parietal focus represented by isolated medium-voltage spikes.

DISCUSSION

This partialis status epilepticus, more appropriately defined in this report a case of EPC, represents a rare complication of CSD. Our patient fulfils three out of the four criteria established for the diagnosis of CSD[8], namely, history of exposure to cats, presence of scratches, and positive *B. henselae* specific test. The fourth criterion, i.e. the finding of lymphatic involvement, can only be suspected, as the transitory lymph node swelling and cutaneous rash had been interpreted as a side effect of CBZ treatment rather than a CSD manifestation. Accordingly, no further steps had been taken towards a histological examination of the lymph nodes, and the possible relevance of this finding, which only gives significant results up to a few days[9], was no longer considered.

The mechanism by which *B. henselae* manifests its neurotropism remains elusive, though an immune-mediated vasculitis has been suggested[10] as a causative agent, mainly because the irregular structure of the cerebral vessels, which showed findings similar to that of cerebral autoimmune arteritis, has been described in some patients after ischemic strokes secondary to CSD[11].

The extension and the aspect of MRI findings are not specific though similar to those described in a recent CSD case report[12]. However, though the occurrence of a transient, rapidly changing MRI hyperintensity may reflect modifications occurring in vasculitic tissues, we cannot rule out that this finding may represent the outcome of localised vascular inflammation rather than the inflammation itself[13]. The involvement of the right sensory-motor area in the process may play a role in the 'sensation of extraneity' experienced by

our patient during the EPC which may be regarded as part of the seizure episode. Although in the present case a specific immune-mediated aetiology should be considered unlikely since common autoantibodies were negative, nonetheless an autoimmune pathogenesis cannot be completely ruled out. It has been suggested that circulating antibodies can induce an immune response by focal disruption of the blood–brain barrier (BBB) and may interact with synaptic receptors structurally similar to bacteria periplasmic amino acid-binding proteins[14]. This penetration mechanism may give access to the neural structure to circulating pathogenic antibodies, promoting an interaction with brain antigens. One possible consequence of the subsequent neural injury could be the induction of seizures. Several experimental[15] and clinical[16] data show that focal seizures induce a further local transient increase in the permeability of BBB, activating a cascade of pathologic events eventually leading to the permanent activation of an epileptic focus. Since encephalitis represents a rare and occasional complication of CSD, it seems likely to hypothesise that in some subjects the disease may induce an unusual autoimmune response. It could be speculated that this mechanism may be raised against specific receptor domains in a similar way as that described within synapses in the pathogenesis of other epileptogenic encephalitis[17] and, depending on the individual reactivity, it could have a role in the activation of the epileptogenic process.

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