A new case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids

Jonathan List,1 Anne Lesemann,1 Edzard Wiener,2 Georg Walter,3 Dominik Hopmann,3 Stephan Schreiber1 and Klemens Ruprecht1

1 Department of Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany
2 Department of Neuroradiology, Charité – Universitätsmedizin Berlin, Berlin, Germany
3 Department of Neurology, Vivantes Klinikum Spandau, Berlin, Germany

Correspondence to: Klemens Ruprecht, Department of Neurology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
E-mail: klemens.ruprecht@charite.de

Sir, We read with great interest the recent article published in Brain by Pittock and colleagues (2010) describing eight patients with a previously unrecognized distinct brainstem encephalitis named chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). Here, we report on what we believe to be another patient with CLIPPERS, lending further support to the concept that CLIPPERS is a novel, definable, inflammatory CNS disease. The patient provided written informed consent for presentation of her case as a report.

A 69-year-old female noticed general weakness, dizziness and abnormal fatigue with subacute onset 16 weeks prior to evaluation at the Department of Neurology, Charité, Universitätsmedizin, Berlin. Eleven weeks prior, the patient developed horizontal diplopia and walking difficulties that gradually worsened so that she became unable to walk without assistance. Additionally, she noticed dysarthria and dysphagia as well as facial tingling and paraesthesia in her fingertips. About 4 weeks prior to admission, she developed hyperacusis and a labile affect with involuntary crying. Her past medical history was unremarkable except for arterial hypertension, which was treated with bisoprolol. Her family history was negative.

Neurological examination on admission revealed a cerebellar syndrome with limb, gait and stance ataxia, as well as intention tremor on the left, more than on the right-hand side. She had marked cerebellar dysarthria. Her gait was wide based and unsteady and she could not walk more than few steps with bilateral support. On horizontal eye movement testing she could only abduct her left eye indicating a one and a half syndrome. The remainder of the neurological examination was normal.

MRI of the brain revealed multiple, small, disseminated, T2 hyperintense lesions in the pons, medulla oblongata, cerebellar peduncles and cerebellar hemispheres with prominent punctate or curvilinear gadolinium enhancement (Fig. 1). Spinal cord MRI demonstrated no extension of the lesions below the upper cervical cord (Fig. 1). CSF analysis was performed 7 and 16 weeks after symptom onset. The first examination showed a normal cell count (2 cells/µl; normal 5–5/µl), normal protein (42 mg/dl; normal range 15–45 mg/dl), and CSF-specific oligoclonal bands. The second CSF examination demonstrated a very mild pleocytosis (6 cells/µl), normal protein (34 mg/dl), but no oligoclonal bands in CSF or serum. Manual CSF cytology did not reveal any malignant cells. DNA polymerase chain reactions in CSF for Herpes simplex virus type 1 and 2, varicella zoster virus, JC virus, as well as mycobacterium tuberculosis complex and Tropheryma whippelii were negative.

Further laboratory work-up revealed a moderate CD4 (420/µl; normal range 500–1200/µl) and CD8 (100/µl; normal range 300–800/µl) lymphopaenia, while the remaining blood count (including total leucocyte count) was unremarkable. Renal and liver function tests were normal. Serological testing excluded borrelia, syphilis and HIV-1 infection. Angiotensin converting enzyme in serum was normal (63 U/l; normal range 15–80 U/l). Serum antibodies against the aquaporin-4 water channel, thyroid peroxidase, thyreoglobulin, glutamic acid decarboxylase, GQ1b and onconeural antibodies (anti-amphiphysin, anti-Ri, anti-Yo, anti-Hu, anti-CV2/CRMP5, anti-Ma2/Ta), as well as anti-cardiolipin immunoglobulin M and immunoglobulin G (IgG) were all negative. Anti-nuclear
antibodies were mildly elevated (1 : 320) and double-stranded DNA antibodies (IgG) were elevated (51 U/ml; normal <20 U/ml). A screen for antibodies against extractable nuclear antigens was negative. Cerebral catheter angiography was normal with no evidence for vasculitis. Computer tomography of the chest and whole body positron emission tomography gave no hint of an underlying malignancy, but revealed clinically asymptomatic pulmonary embolism. Brainstem auditory-evoked responses and motor-evoked potentials were normal; however, somatosensory-evoked potentials showed prolonged latencies bilaterally.

A diagnosis of CLIPPERS was made and the patient was treated with 1000 mg methylprednisolone per day intravenously for five consecutive days and subsequently with 60 mg methylprednisolone per day orally. Within 1 week after start of corticosteroids, dysarthria and ataxia markedly improved and the patient became able to walk with a walking frame. Hyperacusis and paraesthesia completely resolved. A brain MRI performed 1 week after the first corticosteroid administration showed marked reduction in gadolinium enhancement of the brainstem and cerebellum and a decreased T2 lesion load (Fig. 1). Repeat somatosensory evoked potentials had returned to normal. The patient was started on methotrexate (7.5 mg/week) and methylprednisolone was slowly tapered. On the last follow-up examination, 9 weeks after initiation of corticosteroid therapy, the patient reported mild

**Figure 1** Brain (A, B, D, G) and upper spinal cord (C) MRI performed 8 weeks after symptom onset show multiple, small, T2 hyperintense lesions disseminated in the pons, medulla oblongata, cerebellar peduncles and cerebellum [sagittal (A) and axial (G) T2-weighted images] with prominent punctate or curvilinear gadolinium enhancement [coronar (B) and axial (D) post-contrast T1-weighted images]. Spinal cord MRI demonstrates lesions in the upper cervical cord [sagittal post-contrast T1-weighted images (C)]. Follow-up brain MRIs were performed 16 weeks after disease onset, i.e. immediately before initiation of corticosteroid therapy (E, H), and 1 week after corticosteroids were started (F, I). Whereas the disease process was still active before corticosteroid therapy (E, H), a marked reduction in gadolinium enhancement (F) and a decrease in T2 lesion load (I) was observed following corticosteroid therapy.
unsteadiness but was well otherwise. She could walk without assistance and neurological examination was unremarkable except for mild gait ataxia.

The clinical and MRI findings of the patient described herein are highly reminiscent of the previously reported findings in the original series of eight patients with CLIPPERS (Pittock et al., 2010), strongly suggesting that our patient suffers from the same disease. This is further supported by the good clinical and radiological response to corticosteroid therapy that was similarly observed in the original patient series. Extensive diagnostic work-up could largely rule out alternative diagnosis such as neurosarcoidosis, Bickerstaff encephalitis, CNS vasculitis and infectious or (para)neoplastic CNS diseases. Brain biopsies performed in four of the eight patients reported by Pittock et al. (2010) consistently demonstrated predominantly T-lymphocytic white matter perivascular and parenchymal infiltrates. However, we felt that in our case, a brain biopsy was not warranted, given the typical clinical and radiological features of CLIPPERS. Although the pathogenesis of CLIPPERS is currently unknown, it appears to be an immune-mediated disease. In this respect, detection of CSF-specific oligoclonal bands that disappeared on follow-up CSF examination is interesting and seems compatible with a dynamic immune-mediated process. The significance of the moderate panlymphophaenia and somewhat elevated anti-nuclear and double-stranded DNA antibodies remains unclear. However, elevated anti-nuclear antibodies and double-stranded DNA antibodies have also been observed in patients with another immune-mediated CNS disease, neuromyelitis optica (Pittock et al., 2008), and may thus be considered an unspecific phenomenon associated with these immune-mediated disease processes.

References