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Short communication

Atypical chronic lymphocytic inflammation with pontocerebellar perivascular enhancement responsive to steroids (CLIPPERS), primary angiitis of the CNS mimicking CLIPPERS or overlap syndrome? A case report

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ABSTRACT

A novel type of encephalomyelitis was first described as chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) in 2010 and few additional patients were reported since then. Partially due to its unknown aetiology and a lack of pathognomonic features some have suggested that CLIPPERS may not represent a distinct disease, but rather a syndrome with different underlying aetiologies. Here we report a 49-year-old German female who presented with a number of clinical and paraclinical features described as typical for CLIPPERS, while additionally showing symptoms and findings compatible with primary angiitis of the CNS (PACNS). This case may establish a previously unnoted link between two poorly understood autoimmune conditions of the CNS.

1. Introduction

A novel type of brainstem-predominant encephalomyelitis was first described in 2010 as chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) [1]. CLIPPERS was considered as a distinct disease of unknown aetiology by its original describers. Its key features are: 1) episodic, subacutely progressive cerebellar ataxia as a cardinal symptom as well as diplopia and dysarthria in the majority of cases [1–3], 2) characteristic bilateral, multifocal punctate or curvilinear gadolinium-enhancing MRI lesions, predominantly affecting the pons and extending into adjacent brain regions, 3) white matter perivascular lymphohistiocytic infiltrates, dominated by CD4+ T cells and macrophages, with a variable extent of parenchymal inflammation, 4) steroid responsiveness of the symptoms, and 5) the absence of evidence for alternative diagnoses. In their recent series of five patients, Simon et al. expanded the clinical and paraclinical phenotype of CLIPPERS [2]. They described progressive cognitive impairment, diffuse cerebral atrophy, MRI lesions predominantly affecting the cerebellum, and significant axonal damage in biopsy specimens as novel facultative findings in CLIPPERS patients. In accordance with their MRI findings, they suggested to rename the syndrome to chronic lymphocytic inflammation with ponto*cerebellar* perivascular enhancement responsive to steroids. Based on the absence of a specific biomarker and potential similarities of CLIPPERS to other autoimmune conditions, such as Sjögren's syndrome or Behcet's disease, it was suggested that CLIPPERS may represent a syndrome with different aetiologies rather than a distinct disease [4]. Here we report on a patient who showed core features of CLIPPERS, but additionally had findings compatible with primary angiitis of the CNS (PACNS), a heterogeneous autoimmune syndrome of the CNS with unknown aetiology [5]. It currently remains open whether this patient had atypical CLIPPERS, PACNS mimicking CLIPPERS or an overlap syndrome between both conditions.

2. Case report

In February 2008, a 45-year-old woman subacutely developed mild gait unsteadiness and fluctuating double vision, accompanied by intermittent nausea and dizziness. Neurological examination in March 2008 revealed mild ataxia of gait and stance and was reported as otherwise normal. A cranial MRI showed roughly symmetrically distributed T2-hyperintense and contrast-enhancing lesions scattered throughout

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the brainstem, cerebellum, basal ganglia and the cerebral white matter. The most affected area was the cerebellar white matter, while the pons showed only minor involvement (Fig. 1A). A CT angiography was reported as normal. CSF examination demonstrated mild lymphomononuclear pleocytosis (11 cells/μl; normal<5/μl), an elevated protein level (77.4 mg/dl, normal<50 mg/dl), CSF-specific oligoclonal bands and a negative intrathecal, polyspecific antiviral immune response. Serum and CSF angiotensin converting enzyme and β2-microglobulin levels were normal and chest radiography was unremarkable. A vasculitis screening and extensive infectiological investigations were negative. Based on the assumption of an immune-mediated acute encephalomyelitis, 1000 mg methylprednisolone per day intravenously was administered over 5 days, which induced a complete clinical remission within a few days.

After a stable cranial control MRI in June 2008, which however still demonstrated multifocal gadolinium enhancement, the patient again subacutely developed gait unsteadiness and in addition progressive occipital headache of pressing quality with an intensity of 8–9/10 on a visual analogue scale. Her previous headache history was unremarkable. On first admission to our department at the end of July 2008, neurological examination revealed mild cerebellar ataxia of gait and stance, mild dysmetria of her left arm, saccadic eye movements and an impaired horizontal optokinetic nystagmus to the left and the right. As in all subsequent neurological examinations, no dysarthria was noted. A cranial MRI showed a reduction of lesion numbers in all affected areas but a slight increase in size of the cerebellar lesions. Digital subtraction angiography (DSA) demonstrated a circumscribed narrowing of the left vertebral artery (Fig. 1C) and slight focal narrowing of branches of the left anterior cerebral artery (Fig. 1D). CSF examination revealed 10 cells/μl, a protein level of 50 mg/dl and CSF-specific oligoclonal bands. Flow cytometry of CSF cells demonstrated predominantly mature CD3-positive T cells and a CD4/CD8 ratio within the upper normal range (4.2, normal<5). Vasculitis screening, onconeuronal antibodies and an extensive tumour search including a CT scan of thorax and abdomen, which also did not provide evidence for sarcoidosis, and a whole body FDG positron emission tomography scan were negative. Multimodal evoked potentials were normal. Another high-dose steroid pulse therapy over 5 days induced a complete clinical remission. Cyclophosphamide pulse

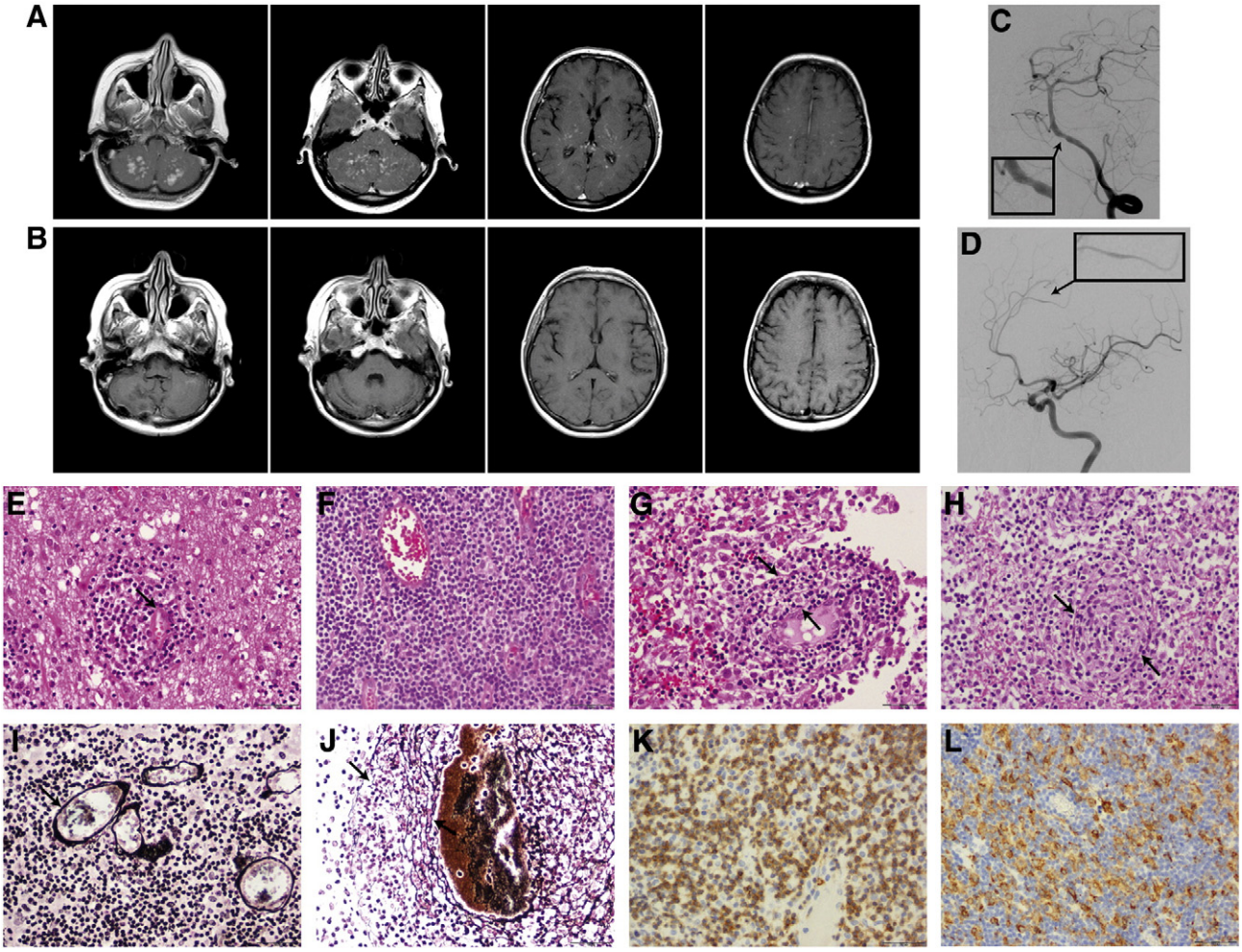

Fig. 1. Neuroimaging and neuropathological findings. (A) T1-weighted cranial MRI images show diffuse multifocal areas of enhancement after i.v. application of gadolinium-DTPA, "peppering" the white matter of the cerebellum, brain stem, basal ganglia and supratentorial region with a clear accentuation in the cerebellum. (B) The latest MRI shows a complete resolution of enhancement. A defect after bleeding and biopsy of the right cerebellar hemisphere and a slight cerebellar atrophy are remaining. (C, D) Digital subtraction angiography: (C) The oblique projection of a selective left vertebral artery injection shows a slight but definitive short narrowing of the arterial lumen (insert) just below the base of the basilar artery in an otherwise completely normal vessel. (D) Selective left carotid artery injection demonstrates a slight focal beading and narrowing of a branch of the left anterior cerebral artery (insert). (E–L) Neuropathological findings from a stereotactic cerebellar biopsy. (E–H) Haematoxylin and eosin (H&E) stainings demonstrate intense perivascular (E, vessel wall indicated by arrow) and parenchymal lymphocytic infiltrates, showing sheets of inflammation in most affected areas (F). Single vessels reveal a transmural lymphocytic infiltration (G, split vessel wall delineated by arrows) or even an occlusion of vessels due to inflammation (H, vessel indicated by arrows, no vessel lumen visible). The Gomori silver stain correspondingly reveals mostly intact vessels (I) with single vessels showing split walls (J, indicated by arrows). Inflammatory infiltrates are predominantly composed of CD3-positive T cells (K) and of KiM1P-positive macrophages (L). Scale bars: 100 μm.