Case Report

Recurrent Monofocal Demyelinating Disease

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Summary

We describe a patient with recurrent brainstem symptoms and migraine-like headache. Magnetic resonance imaging (MRI) showed a symptomatic hyperintense T2-weighted lesion in the middle cerebellar peduncle and the trigeminal nuclei and an asymptomatic periventricular lesion of Dawson finger shape. The findings were suspicious for a first demyelinating event, possibly representing the first manifestation of multiple sclerosis (MS). Nevertheless, this case report also illustrates several pitfalls in the differential diagnosis of MS.

KEY WORDS:
MULTIPLE SCLEROSIS; POST-INFECTION ENCEPHALITIS; MIGRAINE-LIKE HEADACHE; BRAINSTEM LESION

Introduction

The damage of myelin sheaths and myelin-supplying cells (demyelination) occurs in various diseases of the central nervous system (CNS) with ischaemic, metabolic, genetic, infectious or autoimmune aetiologies.1 Autoimmune demyelinating CNS diseases may be postinfectious (e.g. acute disseminated encephalomyelitis [ADEM]) or idiopathic (e.g. multiple sclerosis [MS]). Their disease course is monophasic, recurrent (relapses always show the same clinical presentation) or multphasic (relapses indicate involvement of new CNS areas), mono- or multifocal. Hence, autoimmune demyelinating CNS diseases may be i) monophasic multifocal (e.g. ADEM), ii) recurrent multifocal (e.g. recurrent ADEM), iii) multphasic multifocal (e.g. MS), iv) monophasic monofocal (e.g. idiopathic optic neuritis, idiopathic transverse myelitis) and v) recurrent monofocal (e.g. recurrent optic neuritis, recurrent transverse myelitis). Here we report a case with an uncommon recurrent monofocal course of a demyelinating CNS disease presenting with brainstem symptoms.

Presentation of Case

On 12 December 2005, the 32-year-old male patient woke up in the night due to severe right-sided nuchal-occipital headache lasting for about 4 hours accompanied by nausea and vomiting. The headache intensity and its weak response to non-steroidal anti-inflammatory drugs was reported to be different from the known migraine with visual aura. A few hours later, hypaesthesia of the right face was perceived. The patient was hospitalized after worsening of the sensory deficits over the following five days. Neurological examination revealed (i) dissociated sensory disturbance with right-sided hypaesthesia and left-sided hypalgiesia of the second and third branches of the trigeminal nerve and (ii) mild horizontal nystagmus on left gaze. All symptoms resolved spontaneously and completely within 3 weeks. Brain magnetic resonance imaging (MRI) detected a hyperintense lesion (6.5x13 mm) on diffusion-weighted (DWI), T2-weighted and fluid attenuated inversion recovery (FLAIR) images in the region of the right middle cerebellar peduncle (MCP) and the right dorsolateral pons with affection of the trigeminal nuclei (Figure 1A). In addition, a periventricular lesion (8x3 mm) with Dawson finger shape, characteristic for MS, was visible (Figure 1B). None of the lesions showed gadolinium enhancement. Cerebrospinal fluid (CSF) was clear and showed normal cell count, protein, IgM, IgA and IgG indices. Oligoclonal bands (OCB) were negative.
On 20 January 2006, the patient was readmitted for right-sided headache (6 hours) with nausea and vomiting and subsequent hypesthesia of the right face (full recovery after 2 weeks). The character of the headache was indicated as very similar to the one 5 weeks ago but different to the usual migraine attacks. Findings on neurological examination, brain MRI and CSF were unchanged compared with December 2005.

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Case Report

Key Points
- Unusual manifestations of CIS lead to great difficulties in differential diagnosis
- Migraine-like headache may be the clinical manifestation of an acute idiopathic inflammatory demyelinating brainstem lesion
- Recurrence of relapse symptoms within 3 months from the initial clinical event may be related to the same acute monophasic inflammatory process
- New or active idiopathic inflammatory demyelinating lesions may be longer detectable on diffusion-weighted than Gd-enhanced MR images

Figure 1. MRI at the time of the initial event. 
(A) Symptomatic lesion in the region of the right MCP and the right dorsolateral pons with increased signal intensity on DWI, T2-weighted and FLAIR images and no gadolinium-enhancement. 
(B) Asymptomatic T2 and FLAIR hyperintense periventricular lesion of Dawson finger shape.

The last admission was on 16 February 2006. This time the patient reported an initially strong fatigue which made him sleep for 30 hours without a break. Thereafter, he felt numbness on the right side of the lip, tongue and oral mucosa. About 5 days later, a rotatory vertigo to the left with nausea and vomiting developed. Neurological examination showed (i) hypesthesia of all three sensory branches of the right trigeminal nerve, (ii) a non-rotatory spontaneous horizontal nystagmus to the left and (iii) body lateropulsion to the right. A prompt and complete remission of the symptoms was achieved by intravenous injection of methylprednisolone (1 g/day for 3 days). In comparison with the initial findings, brain MRI and CSF revealed no changes except for a slight CSF pleocytosis (9 cells/μl). 

Extensive paraclinical testing was performed during the three hospital stays. No abnormalities were found on (i) multimodal evoked potentials (VEP, BAEP, upper and lower limb SEP and MEP), (ii) coagulation tests, (iii) neurovascular assessment (transoesophageal echocardiography, electrocardiography, extra- and intracranial neurovascular ultrasound, MR angiography), (iv) infectious assessment (PCR/antibody titres in serum and CSF against borrelia, listeria, treponema pallidum, toxoplasma; VCV, HSV-1, HSV-2, HIV, HAV, HBV, HCV, EBV, CMV, adeno-, entero-, echo, rubella, mumps-, measles-virus) and (v) immunological tests (chest CT and ACE, ANA, rheuma factor, c-ANCA, p-ANCA, antibodies against double-stranded DNA, antibodies
against the Sm antigen, antiphospholipid antibodies in serum).

The patient suffered no further symptoms during the follow-up period (until October 2007). A follow-up MRI scan was performed in March 2007. The brainstem lesion was still visible on T2-weighted images with reduced signal hyperintensity, but unaltered size compared with previous scans. However, on FLAIR images, an unequivocal identification of the lesion was no longer possible (Figure 2A). The periventricular lesion was still visible and unchanged in signal intensity and size (Figure 2B).

Discussion

The patient suffered three episodes of clinical exacerbations with monosymptomatic presentation at intervals of 1 month. Each time he reported a gradual onset of trigeminal hypeaesthesia and a sudden onset of migraine-like headache or vertigo. The relapsing symptoms (migraine-like headache, right-sided trigeminal hypeaesthesia, vertigo, nystagmus, body lateropulsion, nausea and vomiting) were fully attributable to the MRI brainstem lesion (Figure 1A). The lesion affected (i) the pontine tegmentum and trigeminal nuclei which are supposed to be involved in the pathogenesis of migraine-like headache and generate trigeminal hypeaesthesia and (ii) the vestibular nuclei and the MCP causing contraversive vertigo and nystagmus, ipsiversive body lateropulsion, nausea and vomiting.

CIS, Possible MS or Recurrent Monofocal Encephalitis?

Several reasons argue for a demyelinating CNS disease of autoimmune aetiology in the present case. The symptoms appeared over at least 24 hours and were preceded by clinical stability or improvement for about 30 days, thus fulfilling the definition of MS relapses by Schumacher et al. and providing clinical evidence of dissemination in time. The gradual onset of symptoms corresponds to the common temporal dynamics of symptom development in inflammatory diseases. In addition, the symptoms responded well to treatment with high-dose methylprednisolone as it is known for autoimmune disorders. Brain MRI demonstrated two lesions, one symptomatic and one asymptomatic. The size and site of the symptomatic MRI lesion was consistent with, and the clinically silent lesion was characteristic for, MS due to its periventricular location and Dawson finger shape. Thus, the paraclinical criteria of dissemination in space would have been fulfilled if OCB in the CSF were demonstrated. Then, in the absence of better explanations, the diagnosis of definite MS would have been appropriate according to the revised McDonald criteria. In the present case, however, one diagnosis could be “possible MS” because OCB in the CSF were negative, but the clinical presentation was repetitive and suspicious for MS. Alternatively, in analogy to other limited forms of idiopathic autoimmune demyelinating diseases as recurrent optic neuritis or recurrent transverse myelitis, the clinical presentations of this case could be subsumed under the diagnosis of “recurrent monofocal encephalitis”, “recurrent brainstem encephalitis” or more descriptive under “recurrent brainstem syndrome”. One might also propose a “clinically isolated syndrome” (CIS) if the episodes of

Figure 2. MRI 15 months after the initial event. (A) The former symptomatic infratentorial lesion is visible on T2-weighted, but not FLAIR images. (B) The asymptomatic periventricular lesion is unchanged on T2 and FLAIR images compared with previous scans.
clinical exacerbations, occurring within the first 3 months from the initial event, were considered as a consequence of one prolonged relapse. However, according to Brex et al, our patient has a high risk of 89% for conversion to clinically definite MS (CDMS) within 14 years due to one asymptomatic MRI lesion. CSF findings were not included in the risk calculation of Brex and colleagues but a recent study demonstrated that the risk of CIS to convert to CDMS is relevantly reduced in the absence of OCB.

New or active MS lesions often show gadolinium enhancement or increased signal intensity on DWI. In the present case, the symptomatic infratentorial lesion was not gadolinium-enhancing but DWI-positive during all three clinical exacerbations. One possible explanation for the lack of gadolinium enhancement might be the initially delayed admission 5 days after symptom onset. Gadolinium-enhancing lesions are supposed to represent a focal breakdown of the blood-brain-barrier (BBB) which is an early event in the development of MS inflammation. There is some evidence that, with increasing time intervals between symptom onset and MRI acquisition, the sensitivity in depicting acute MS lesions decreases more rapidly on T1-weighted images after gadolinium application than diffusion-weighted images. The following relapses might be rather the result of focally reinforced ongoing inflammatory activity, insensitive to gadolinium enhancement, than of a new BBB breakdown promoting the migration of new inflammatory cells into the CNS.

**Differential Diagnosis**

Monophasic and recurrent ADEM or postinfectious encephalomyelitis were important differential diagnoses. ADEM is far more common in paediatric patients, but also occurs in adults. A recent viral infection or vaccination usually induces the characteristic multifocal clinical presentation with encephalopathic symptoms (e.g. drowsiness, seizures, confusion). MRI typically shows multiple, large and gadolinium-enhancing lesions. Unusual cases of ADEM confined to the brainstem have been reported, but in contrast to the present case, all of them presented with a massive and gadolinium-enhancing brainstem lesion. In addition, the asymptomatic periventricular lesion is commonly seen in MS but not in ADEM. Thus, ADEM was unlikely in our patient.

He had a history of migraine with visual aura (three to four attacks per year). The prevalence of supra- and infratentorial (mostly pontine) hyperintense and FLAIR lesions is increased in migraineurs, likely due to small vessel involvement. On the other hand, the pontine part of the trigeminal nucleus pars caudalis is supposed to play a key role in eliciting migraine headache. “Migrainous stroke” is characterized by a sudden onset of a (ischaemic) deficit. This did not apply to our patient and is why we regard a lacunar migrainous infarction as less probable than CIS. Again, the second ovoid periventricular MRI lesion is by far more common in MS.

Migraine is often one of the presenting symptoms in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS). In CADASIL, T2-weighted and FLAIR hyperintense brainstem lesions are frequent. However, our patient had no positive family history of cerebral ischaemic events, showed no signs of cognitive decline and, on brain MRI, multiple and confluent hyperintensities on T2 and FLAIR were not detectable, which is unusual for CADASIL and MELAS. Again, the gradual onset and recurrence of the monofocal symptoms is atypical for strokes. Finally, the MRI lesion site at the junction of the dorsolateral pons and cerebellum did not conform to a vascular territory or a typical site of lacunes. These considerations and the lack of evidence for an ischaemic pathogenesis in our extensive paraclinical testing also argue against systemic vasculitides, vertebral artery dissection and primary CNS angiitis.

Infectious diseases were unlikely in consideration of the spontaneous remissions, good response to steroid treatment and normal infectious serological and CSF workup. No evidence was found for neurosarcoidosis (normal serum ACE and chest CT). The relapsing clinical presentation and MRI findings were incompatible with adult onset leukodystrophies. CNS neoplasm such as glioma and lymphoma were implausible on the basis of the spontaneous remissions and the regressive MRI follow up.
In summary, we propose that our patient suffered a CIS with brainstem symptoms. The clinically silent periventricular MRI lesion with MS-characteristic Dawson finger shape was inconsistent with recurrent brainstem encephalitis and suggests a relevant risk for conversion to CDMS. Supported by the stable clinical and MRI findings on follow-up, the recurrence of the brainstem symptoms was preferably related to the same acute monophasic condition. Alternatively, pseudo-relapses might have explained the recurrence of symptoms. However, this was unlikely because the main causes of pseudo-relapses (fever, infections) were not present. It is unclear if a CIS with recurrent symptoms within the first 3 months from the initial event is associated with a higher risk for conversion to CDMS than the usual non-recurrent CIS event is associated with a higherrisk for conversion symptoms within the first 3 months from the initial event. In any case, we believe that the initiation of MS-specific immunotherapy was not indicated due to the low MRI lesion load, the negative CSF and normal multimodal evoked potentials.

Conflicts of Interest
No conflicts of interest were declared in relation to this article.

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