Clinical Case Report

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Relapsing–remitting lesions in a woman with progressive hemifacial atrophy and chronic hepatitis B virus infection

A case report

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Abstract

Introduction: Progressive hemifacial atrophy (PHA) is a rare disorder characterized by unilateral facial atrophy affecting the skin, subcutaneous tissue, and fat, muscle, and osteocartilagenous structures creating a sunken hemiface appearance.

Etiopathogenesis of PHA is poorly understood; no definitive treatment is currently available.

Clinical Findings: We report a 41-year-old woman with PHA who showed an uncharacteristic "relapsing–remitting" evolution of brain lesions and was seropositive for hepatitis B virus (HBV). She presented with a history of recurrent tonic-clonic seizures. Magnetic resonance imaging (MRI) showed progressive atrophy and multiple white matter lesions in the left side of the brain. Interestingly, the serial MRI examination (4 MRI scans over a period of 9 years) showed a "relapsing–remitting" pattern of brain lesions akin to that observed in a subtype of multiple sclerosis. Autoimmune-related investigations revealed increased serum levels of immunoglobulin (Ig) G, anti-nuclear antibody (ANA), and γ-IgG. Infection is considered as one of the possible causes of PHA. However, the association of peripheral infection such as HBV infection with PHA has not been reported.

Conclusion: Our experience with this case suggests that PHA may have a relapsing–remitting disease course. Autoimmune inflammatory response to chronic HBV infection may have triggered the relapse in this case. This case underlines a novel etiopathogenetic mechanism of PHA.

Abbreviations: ADEM = acute disseminated encephalomyelitis, ANA = antinucleic antibody, BBB = blood–brain barrier, CNS = central nervous system, CSF = cerebral spinal fluid, DSA = digital subtraction angiography, EEG = electroencephalography, HBeAg = HBV envelope antigen, HBsAg = HBV surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, Ig = immunoglobulin, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, MS = multiple sclerosis, PHA = progressive hemifacial atrophy, SLE = systemic lupus erythematosus.

Keywords: autoimmune, HBV, inflammation, progressive hemifacial atrophy, relapsing–remitting lesions

1. Introduction

Progressive hemifacial atrophy (PHA) (also referred to as the Parry–Romberg syndrome) was first reported by Parry in 1825, and, later, described in more detail by Moritz Heinrich Romberg (1846).[1] It is a rare disorder that usually presents in the first or second decade of life and is characterized by unilateral atrophy of the face and subcutaneous tissues. Sometimes, the condition may affect the underlying bony structures.[1,2] In the majority of patients, the disease stabilizes over a period of 2 to 10 years after its first presentation; a small proportion of patients (26%), however, may experience sustained progression.[1] Neurological complications such as epilepsy, migraine, hemiplegia, and trigeminal neuralgia may develop in 15% of all PHA patients.[1,3] Neuroimaging typically reveals unilateral hemisphere shrinkage, white matter lesions, and intracranial calcification.[4] However, longitudinal changes during progression of the disease have rarely been reported.

The etiology of PHA remains poorly understood; defects of vascular supply, trauma, sympathetic over-excitation, and infection have all been postulated as possible causes.[2,5,6] In this report, we describe a case of PHA who manifested serial changes in brain lesions on magnetic resonance imaging (MRI). The case suggests that PHA may have a "relapsing–remitting" disease course and that periphery hepatitis B virus (HBV) infection associated auto-immune inflammatory process may be one of the triggers for relapse of PHA.

2. Case report

A 41-year-old woman was referred to our department because of recurrent tonic-clonic seizures. Her left side of the face was of

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Ethical approval was obtained from the Ethics Committee from The First Hospital of Jilin University, China. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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smaller size; the deformity was noticed since she was a teenager, and which progressed with increase in age. The first episode of seizures occurred when she was 32 years old. The patient was diagnosed as a case of encephalitis and received acyclovir treatment. The second episode of tonic-clonic seizures occurred at the age of 40 years. A diagnosis of encephalitis-related seizure was made and antiepileptic therapy prescribed. Eight months after the second seizure attack she sustained a third attack and was therefore referred to our department.

She had a history of headache on the left side of the head. Besides, she also had a history of paroxysmal electric discharge like abnormal sensations on the left half of face and memory decline. Her neonatal and family history was unremarkable.

Neurological examination showed facial asymmetry with marked hypoplasia of the left side of the face, left enophthalmos, left eyelid, tongue, gingival and periodontal tissue atrophy, and left teeth crowdedness (Fig. 1G). The left face of this patient was dry but did not show any sclerosis. Her lower left lips were thinner than that at the right side and a big linear dark scar *(coup de sabre)* was observed. The muscle strength of the right lower extremity was 4/5 on Muscle Strength Grading Scale. The pathological reflexes were normal. On electroencephalography (EEG), spike and slow waves were observed over the left temporal area. Cerebrospinal fluid (CSF) examination showed normal cell counts, protein and glucose levels. She tested positive for antibodies against Hepatitis B virus (HBV) surface antigen (HBsAg) and envelope antigen (HBeAg). Immunoglobulin G (IgG) levels were increased both in CSF (51.7 mg/L, normal range: 0–34.0 mg/L) and in the serum (16.4 g/L, normal range: 7–16 g/L). Laboratory tests related to autoimmune function showed higher values of γ-IgG levels (23.1%, normal range: 9.0–18.0%) and lower levels of complement C3 (0.86 g/L, normal range: 0.9–1.8 g/L). The antinuclear acid antibody was positive (1:320, normal range 1:100).

The first MRI scan performed at the time of the first seizure episode showed multiple white matter lesions in the left frontal

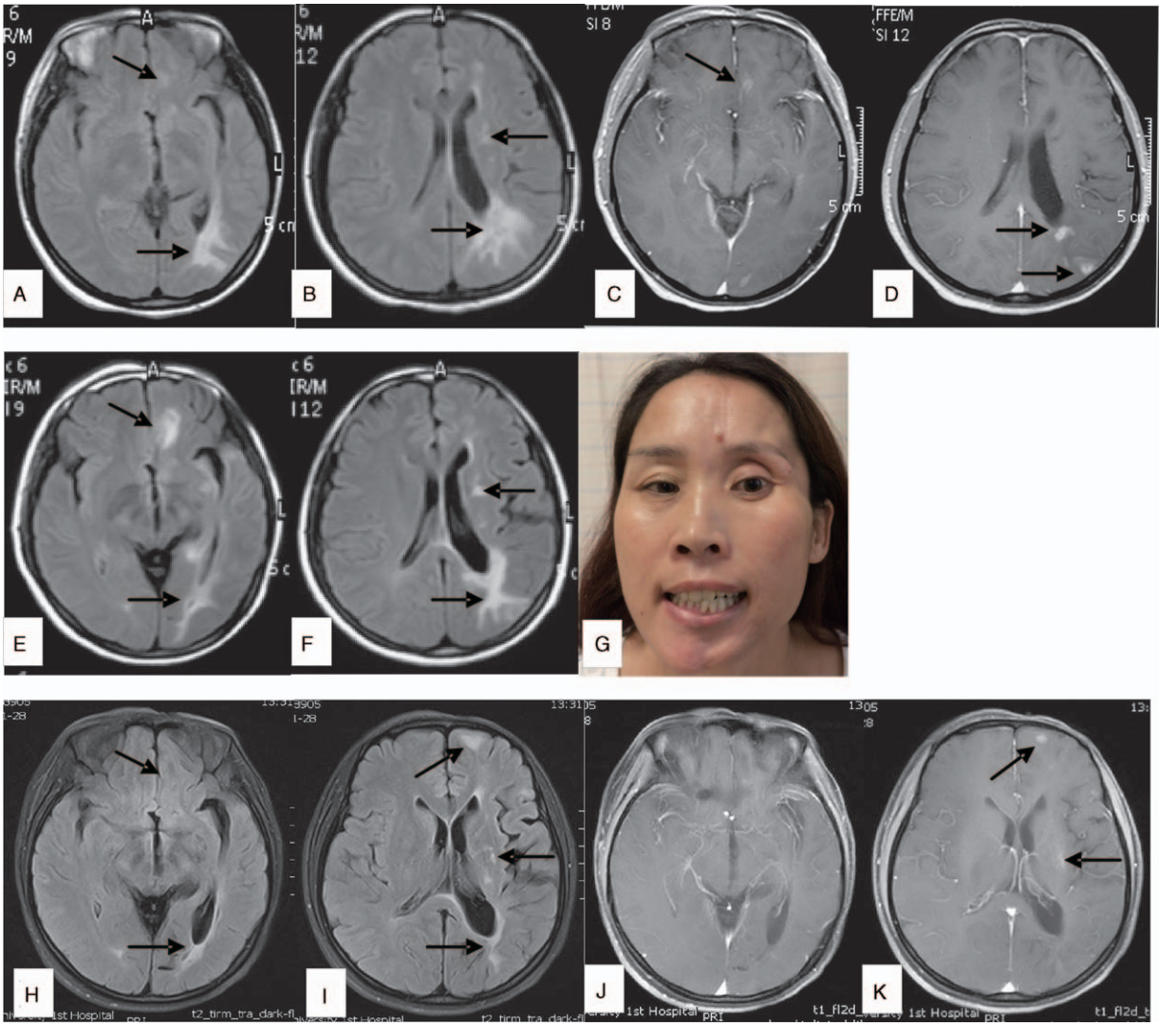

Figure 1. (A–G) MRI axial T2-FLAIR performed in December 2014 showed enlarged left ventricle and multiple hyperintensities in the left frontal, temporal, occipital and parietal lobes and the periventricular area (A and B); some lesions presented heterogeneous enhancement on T1 postcontrast images (C and D). The left ventricle was bigger on MRI axial T2-FLAIR in January 2015; lesions in the left orbitofrontal cortex and the basal ganglia were more widespread, whereas the lesions in the periventricular area were smaller (E and F). In August 2015, the left ventricle enlarged more on MRI, MRI axial T2-FLAIR also showed attenuation of lesions in the left orbitofrontal cortex (H and I) and new lesions in the left superior frontal gyrus (I), some lesions are partially enhanced (J and K). Photograph of the patient (G). FLAIR = fluid-attenuation inversion recovery, MRI = magnetic resonance imaging.

lobe and the parieto-occipital area; some lesions were enhanced after the gadolinium contrast injection (the MRI was lost). The second MRI examination was performed in December 2014, immediately after the second seizure episode. It showed enlargement of the left lateral ventricle and multiple lesions in the left frontal and parietal lobes and the periventricular area (Fig. 1A and B); heterogeneous gadolinium enhancement was observed in the left frontal and parietal lobes (Fig. 1C and D). MRI performed 1 month after the second seizure episode (i.e., in January, 2015) showed that the lesions in the left orbitofrontal cortex and basal ganglia were more widely diffused, whereas the lesions at the periventricular space and the posterior horn of the lateral ventricle had attenuated (Fig. 1E and F). The most recent MRI (August, 2015) showed increase in the size of left ventricle, when compared with previous MRI study performed 7 months ago. Moreover, the lesions in the left orbitofrontal cortex had attenuated and new lesions appeared in the left superior frontal gyrus, some of which are partially enhanced (Fig. 1.H–J). No intracranial vascular abnormalities were identified on magnetic resonance angiography (MRA) or digital subtraction angiography (DSA) (data not shown).

3. Discussion

PHA is characterized by unilateral atrophy of the face, including that of skin and the subcutaneous tissue.[3] Our patient experienced slow progressive atrophy of her left face since her teenage, as evidenced by changes on MRI. Neurological complications such as seizures are known to occur in up to 15% of all PHA patients.[1,7] This patient has a 9-year-long history of recurrent tonic-clonic epilepsy. The EEG showed spikes and slow waves predominantly in the left temporal lobe, which is indicative of seizure activity. Besides, the patient also had a history of migraine, which is a common accompaniment in PHA patients.[2] The clinical picture was consistent with the diagnosis of PHA.

Serial changes in imaging findings with progression of the disease have rarely been reported. In the present patient, 4 MRI examinations performed over a period of 9 years showed progressive left brain atrophy and multiple lesions affecting both white and gray matter in the left hemisphere. Similar cases have been described elsewhere.[4] Interestingly, brain lesions in this patient appeared and resolved, a pattern similar to that associated with a subtype of multiple sclerosis (MS), the relapsing–remitting MS. To date, no disease-modifying drugs are available for PHA. The relapsing–remitting lesions in this patient indicate that identification of triggers for relapse may help prevent the progression of the disease. In MS, relapses are believed to represent recurrent episodes of inflammation and demyelination that are often accompanied by axonal injury.[8] Immune cell-infiltration in the central nervous system (CNS) and microbial infections have been considered as immunological triggers for relapse in MS,[8] all of which can elicit an inflammatory response. Typical histological findings in patients with PHA include epidermal atrophy, inflammatory infiltrate, gliosis, and neuronal loss.[1,9] Therefore, it is plausible that the "relapsing–remitting" lesions in this patient may have similar inflammatory background. Some brain lesions of this patient showed gadolinium enhancement, which indicates disruption of the BBB and inflammation. After excluding the possibility of brain tumor and vascular malformations by MR spectroscopy and DSA analysis, we think the enhancement of lesions might be related to vasculitis. Indeed, perivascular inflammation and microglial activation have been reported in a PHA patient with epilepsy at brain biopsy,[9] which suggests that inflammation can be one of the factors that drive the acceleration of PHA.

One of the common causes of inflammation is infection. Interestingly, this patient tested positive for antibodies against HBs Ag and HBe Ag. Various infections such as *Borrelia burgdorferi*,[10,11] poliomyelitis,[12] and Herpes Zoster[13] have been reported in patients with PHA. However, patients with concomitant HBV infection and PHA have not been reported. Chronic HBV infection can cause persistent hepatic inflammation and cirrhosis.[14] However, neurologic complications of HBV such as acute disseminated encephalomyelitis (ADEM)[15] and Guillain Barré syndrome have also been noticed, which suggests that periphery disease can affect the brain.[16,17] In addition, HBsAg has been identified in the CSF of patients without active liver disease but with positive HBsAg in serum.[18]

For a long period of time, the blood brain barrier (BB) was thought to protect brain from infections in the periphery. It has been controversial whether HBsAg crosses BBB from the periphery or if it is locally generated within the CNS. One possible explanation could be a change in the permeability of the BBB.

On the other hand, recent studies suggest that there are intensive communications between the periphery and CNS.[19,20] The molecular mimicry between HBV DNA and myelin proteins and the subsequent activation of autoimmune inflammatory cells could constitute the other possible underlying mechanisms of neurological injury in this patient.[15,16]

Inflammation can also be caused by autoimmune diseases. Concomitant occurrence of autoimmune diseases such as systematic lupus erythematosus (SLE) and PHA has been reported.[1,6] Autoimmunity-related antibodies are often found positive in PHA patients.[21–23] In line with previous reports, increased serum levels of ANA and γ IgG were observed in this patient, which suggests a common autoimmune-related background. Therefore, it is highly likely that the inflammatory microenvironment induced by infection or dysregulated autoimmunity may render the patient more susceptible to PHA.

Surgical aesthetic treatments of hemifacial atrophy such as augmentation of the atrophic region and restoration of the symmetry of the face have been used in clinics.[24,25] However, these treatments do not have a long-lasting effect. Treatment that can halt the disease process is needed. Beneficial effect of immunosuppressive drugs on a PHA patient with cerebral involvement have been reported.[26] The present case showed inflammatory relapsing and remission lesions on MRI. Whether anti-inflammatory and immune suppressive drugs can halt or slow down disease progression is worth further investigation.

In summary, our experience indicates that PHA may have a relapsing–remitting disease course. The autoimmune inflammatory process due to chronic HBV infection may be one of the triggers for relapse. To date, no effective treatment is available for PHA. Elucidation of the etiopathogenetic mechanisms underlying PHA may shed light on novel treatment strategies.

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