

## Case Report

# Primary progressive multiple sclerosis coexisting with patent foramen ovale: a case report

Yun Cheng<sup>1\*</sup>, Chenhong Lin<sup>1,2\*</sup>, Hongliang Zhang<sup>1\*</sup>, Jinming Han<sup>1</sup>, Jie Zhu<sup>1,2</sup>, Tao Jin<sup>1</sup>

<sup>1</sup>Department of Neurology and Neuroscience Center, The First Hospital of Jilin University, Changchun, China;

<sup>2</sup>Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Stockholm, Sweden. \*Equal contributors.

Received April 1, 2016; Accepted July 3, 2016; Epub August 15, 2016; Published August 30, 2016

**Abstract:** Background: Observational data has reported associations between patent foramen ovale and some neurologic events, such as cryptogenic stroke and migraine. However, the coexistence of primary progressive multiple sclerosis and patent foramen ovale has not been documented in literature. Objectives: To report a rare case of primary progressive multiple sclerosis coexisting with patent foramen ovale and to analyze the possible underlying mechanisms between these two conditions that have long appeared to be unrelated. Methods: We describe a patient with a prior diagnosis of primary progressive multiple sclerosis, who was later discovered to be carrying a clinically silent patent foramen ovale. A retrospective review of the literature was performed using the PubMed database. Results: The patient had been carrying clinical silent patent foramen ovale when we diagnosed him as primary progressive multiple sclerosis, which may have led to his low blood pressure and some changes in the serum. Here we offer two possible pathophysiological mechanisms underlying the crosstalk between these two conditions: the hypoperfusion caused by the right-to-left cardiac shunts and the increased blood concentrations of the vasoconstrictive compound serotonin. Conclusions: We speculate that PFO might be a triggering factor for PPMS and further studies are encouraged.

**Keywords:** Primary progressive multiple sclerosis, patent foramen ovale, serotonin, cerebral hypoperfusion

## Introduction

As a rare subtype of multiple sclerosis, primary progressive multiple sclerosis (PPMS) is characterized by a gradual, steady and relentless functional decline from onset, such as impaired walking due to steadily worsening spastic paraparesis, progressive urinary urgency and incontinence as well as gradual cognitive decline [1]. However, like other types of MS, the precise etiology of PPMS still remains unknown.

The patent foramen ovale (PFO) is a common, usually benign, anatomical variant that in the presence of a discrete right-to-left shunt and other predisposing factors, such as Eustachian valve/Chiari network, atrial septal aneurysm, and coagulation cascade abnormalities, may lead to paradoxical embolism, observed at different levels, for instance, cryptogenic stroke, peripheral embolism, coronary embolism, etc [2].

To the best of our knowledge, this is the first reported case of PPMS and PFO coexisting, which may lead to discussion about a potential association between these two diseases with posited association being deemed irrelevant in years past.

## Case report

A 47-year-old Chinese man was admitted to our hospital with complaints of progressive bilateral lower limb weakness recently. The weakness had begun in the left lower limb about 10 years earlier, which subsequently spread to the right lower limb 6 years after the onset. Later, the patient began to complain of post-exercise fatigue which is exemplified by that he had to rest for half an hour after walking for 200 meters. As the disease progressed into the 7<sup>th</sup> year, the patient described other symptoms, including: speech difficulty, coughing after eating or drinking and blurred vision. Two years

## Primary progressive multiple sclerosis coexisting with patent foramen ovale

earlier, he underwent the urethral catheterization twice because of the urinary retention.

Neurological examination on admission: blood pressure 96/60 mmHg; heart rate 52 bpm; dysarthria; both horizontal and vertical, fine nystagmus; left-ward deviation of the uvula; proximal paraparesis (+4/+4); brisk deep-tendon reflexes; bilateral positive Babinski's sign and Chaddock's sign; tendon hyperreflexia bilaterally in lower limbs; hypalgesia along the C4 level on both sides; and mild impairments in vibratory sensation.

Most of the laboratory results were irrelevant. Electromyography revealed lesions in somatosensory pathways, which at the same time ruled out the peripheral neuropathy. Examination of the cerebral spinal fluid (CSF) showed normal protein level and IgG index, but an elevated white blood cell count ( $27 \times 10^6/L$ ) and oligoclonal bands were detected.

A MRI study of the brain showed demyelinated plaques in the periventricular area, bilaterally in the centrum semiovale and corona radiata (**Figure 1A-C**), as well as along the corpus callosum (**Figure 1D**) and one lesion in the right cerebellar hemisphere (**Figure 1F-H**). Such radial orientation and the periventricular location of cerebral lesions are typical of multiple sclerosis. However, there was no such lesion observed in the cervical spinal cord MRI (**Figure 1I, 1J**). Visually evoked potentials showed P100 prolonged latency bilaterally, suggesting subclinical optic nerve lesions. Contrast-enhanced transcranial Doppler (cTCD) revealed curtain-like microbubbles (**Figure 1K**), which was classified as the grade III right-to-left shunting, confirming the diagnosis of PFO, according to the grading system proposed by the International Consensus Criteria [3].

In this case, the patient's neurological function had kept deteriorating over the last 10 years after the onset. And all of his neurologic examination, CSF result, MRI study and other test results supported the diagnosis of PPMS based on the 2010 revised McDonald criteria [4].

### Discussion

Primary progressive multiple sclerosis is present in about 10-15% of the patients with multiple sclerosis (MS) and is characterised by the gradual, progressive and relentless deteriora-

tion of neurological function over a span of years [5].

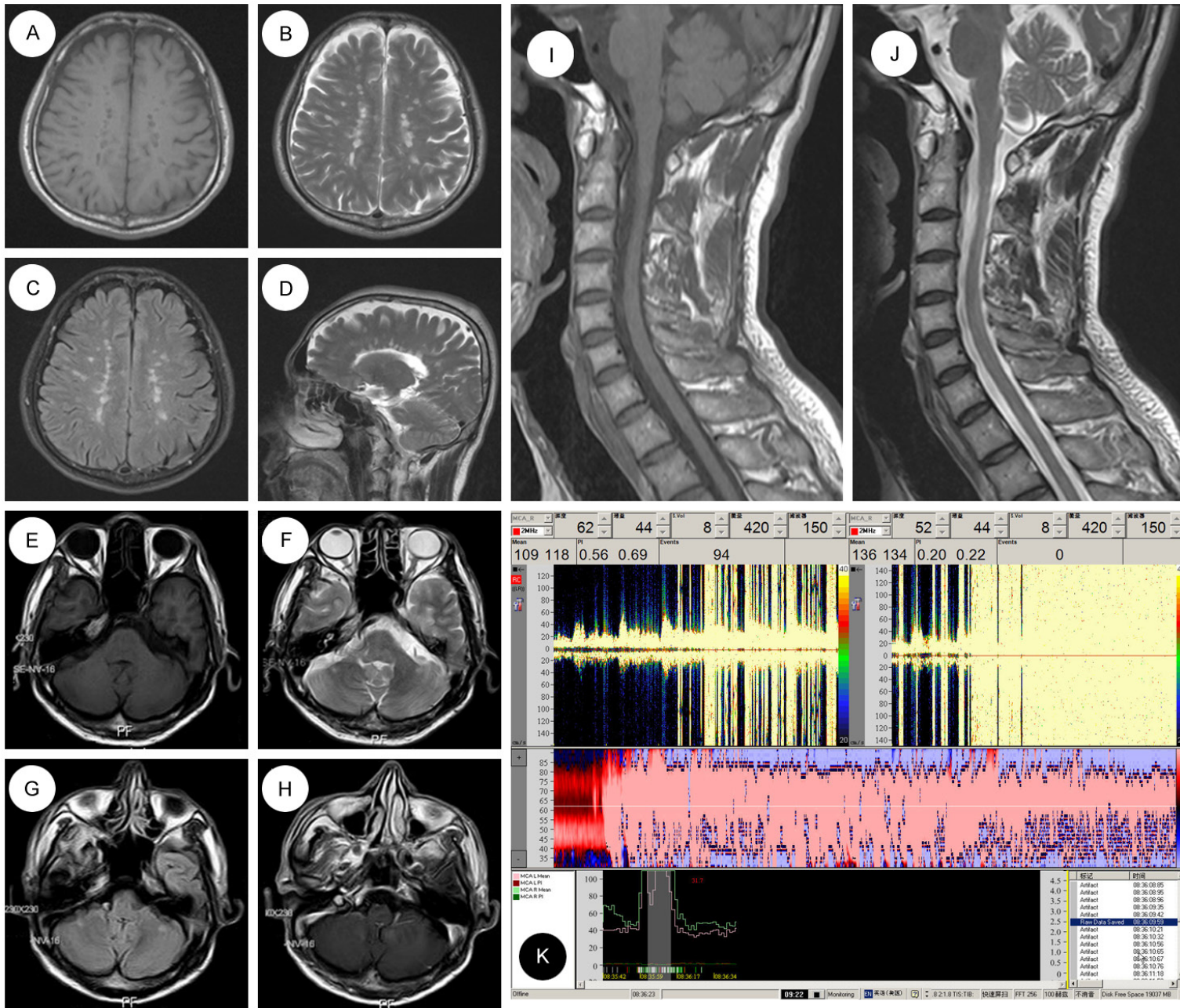
PFO is a relatively common congenital cardiac abnormality and the opening enables communication between the right and left atria. It presents in 25% to 30% of the population, based on autopsy studies [6]. It is considered benign and the asymptomatic patients do not require any specific therapy. On the other hand, PFO is the main cause of right-to-left cardiac shunt followed by pulmonary arteriovenous fistulas, and potentially a risk factor for paradoxical embolism. Other than the subclinical emboli, this right-to-left shunting also allows some potentially harmful metabolites to travel directly from the venous system into arterial circulation, bypassing the pulmonary circulation. One metabolite is serotonin which is normally metabolized by the pulmonary monoamine oxidase (MAO).

Serotonin or 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter, biochemically derived from the essential amino acid, L-tryptophan. It is involved in maintaining the integrity of the blood brain barrier, which is believed to be disrupted in the initial stages when MS symptoms are exacerbated [7].

As PFO can upregulate the serotonin level, PFO concomitant with PPMS implicates dysregulation of the 5-HT system in the pathophysiology of MS. This hypothesis is plausible due to the evidence that treatment of cell recipients with serotonin receptor antagonists effectively blocks both active and adoptively transferred experimental autoimmune encephalomyelitis (EAE) [8]. These effects are partially reversed in the presence of monoamine oxidase inhibitors (MAO-Is); and the 5-HT<sub>1A</sub> receptor antagonist, WAY100635, reduced clinical and histological signs of EAE, and attenuated the adverse effects of the 5-HT<sub>1A</sub> receptor antagonist R(t)-8-OH-DPAT against the severity of the disease.

Chronic cerebral hypoperfusion caused by PFO may be implicated in the development of PPMS as well [9]. Our patient had sinus bradycardia and continuous low blood pressure for a long time, which could later lead to cerebral hypoperfusion. Similar hypoperfusion in the cerebral cortex and subcortical grey matter of patients with MS had been previously reported [13-16]. Such phenomena were initially assumed to be the consequences secondary to

Primary progressive multiple sclerosis coexisting with patent foramen ovale





## Primary progressive multiple sclerosis coexisting with patent foramen ovale

**Figure 1.** Axial T1-weighted image (A), FLAIR (C), T2-weighted image (B) and sagittal T2-weighted image (D) of the brain MRI are indicative of MS demyelination. There are multiple plaques in the periventricular white matter, as seen in the periventricular area, bilateral centrum semiovale, corona radiata, and emanating radially from the corpus callosum (“Dawson fingers”). There is also one lesion in the right cerebellar hemisphere (E-G), which is not shown on the gadolinium-enhanced T1-weighted MRI (H). However, the cervical spine MRI displays no MRI-detected lesions on spinal cord (I, J). On the image of contrast-enhanced transcranial Doppler (K), there reveal curtain-like microbubbles.

the reduced vascular inflow in the context of focal perivascular inflammatory MS lesions [10], or to the increased levels of the vasoconstrictive compound endothelin-1 (ET-1) in blood [11, 12]. However, we argued in this case that PFO might have contributed to the cerebral hypoperfusion, leading to myelin oligodendrocyte destruction and axonal injury in chronic disease conditions, resulting in inflammatory reaction and neurodegeneration.

Therefore, we speculated that PFO may be a triggering factor for PPMS, and of course further study will be required for confirmation.

### Acknowledgements

This work was supported by grants from the Young Scholars Program of the National Natural Science Foundation of China (No. 81301021), General Program of the National Natural Science Foundation of China (No. 81471216), International Science and Technology Cooperation Program of Jilin Provincial Science and Technology Development of China (No. 20150414011GH), Norman Bethune Cultivation Plan of Jilin University (No. 2015320), Science and Technology Program of Jilin Provincial Education Department of China (No. 2016-462), the grants from the Swedish Research Council (K2013-66X-22337-01-3 and project number: 2015-03005), grants from the First hospital of Jilin University, and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (3C113BK73428). We thank Andrew T. Mcallister for his assistance in editing the manuscript.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Tao Jin, Department of Neurology and Neuroscience Center, The First Hospital of Jilin University, 71 Xinmin Street, Changchun 130021, China. Tel: +86 13351505206; Fax: +86 431 88782378; E-mail: drtao.jin@hotmail.com

### References

- [1] Koch MW, Cutter G, Stys PK, Yong VW and Metz LM. Treatment trials in progressive MS [mdash] current challenges and future directions. *Nat Rev Neurol* 2013; 9: 496-503.
- [2] Sathasivam S and Sathasivam S. Patent foramen ovale and migraine: What is the relationship between the two? *J Cardiol* 2013; 61: 256-259.
- [3] Agustin SJ, Yumul MP, Kalaw AJ, Teo BC, Eng J, Phua Z, Singh R, Gan RN and Venketasubramanian N. Effects of Posture on Right-to-Left Shunt Detection by Contrast Transcranial Doppler. *Stroke* 2011; 42: 2201-2205.
- [4] Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinstenker B and Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292-302.
- [5] Miller DH and Leary SM. Primary-progressive multiple sclerosis. *Lancet Neurol* 2007; 6: 903-912.
- [6] Hagen PT, Scholz DG and Edwards WD. Incidence and Size of Patent Foramen Ovale During the First 10 Decades of Life: An Autopsy Study of 965 Normal Hearts. *Mayo Clinic Proceedings* 1984; 59: 17-20.
- [7] Sandyk R and Awerbuch GI. The co-occurrence of multiple sclerosis and migraine headache: the serotonergic link. *Int J Neurosci* 1994; 76: 249-257.
- [8] Dietsch GN and Hinrichs DJ. The role of mast cells in the elicitation of experimental allergic encephalomyelitis. *J Immunol* 1989; 142: 1476-1481.
- [9] D'Haeseleer M, Cambron M, Vanopdenbosch L and De Keyser J. Vascular aspects of multiple sclerosis. *Lancet Neurol* 2011; 10: 657-666.
- [10] Ge Y, Law M, Johnson G, Herbert J, Babb JS, Mannon LJ and Grossman RI. Dynamic susceptibility contrast perfusion MR imaging of multiple sclerosis lesions: characterizing hemodynamic impairment and inflammatory activity. *AJNR Am J Neuroradiol* 2005; 26: 1539-1547.

## Primary progressive multiple sclerosis coexisting with patent foramen ovale

- [11] Speciale L, Sarasella M, Ruzzante S, Caputo D, Mancuso R, Calvo MG, Guerini FR and Ferrante P. Endothelin and nitric oxide levels in cerebrospinal fluid of patients with multiple sclerosis. *J Neurovirol* 2000; 6 Suppl 2: S62-66.
- [12] Pache M, Kaiser HJ, Akhalbedashvili N, Lienert C, Dubler B, Kappos L and Flammer J. Extraocular blood flow and endothelin-1 plasma levels in patients with multiple sclerosis. *Eur Neurol* 2003; 49: 164-168.