Cerebral Hemosiderosis as a Causative Factor of Vascular Parkinsonism

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Abstract- Secondary parkinsonism has comprised about 20 to 40 percent of all parkinsonism patients in movement disorders clinic. Most of them are induced by certain medications. About 5 to 10 percent of these patients are caused by sudden vascular events, who suffer from their parkinsonism abruptly, and usually of aged people with quite apparent stroke risk factors. Hemosiderosis was only occasionally reported as a causative factor in patients with parkinsonism, who presented with an insidious onset parkinsonism and a progressive supranuclear palsy-like clinical picture. We encountered two patients with stroke-related parkinsonism, whose high resolution MRI image showed apparent cortical or intraparenchymal hemosiderosis, although Binswanger type white matter change was also noted. Intracerebral hemosiderosis that manifests clinically as vascular parkinsonism might be much more frequent than we thought.

Key Words: Vascular parkinsonism, Hemosiderosis, Microhemorrhage, Microbleed, Hypertensive microangiopathy

Acta Neurol Taiwan 2005;14:201-207

INTRODUCTION

The disease entity of vascular parkinsonism has been greatly debated for decades[(1)]. It was only briefly mentioned in the eighth edition of The Principles of Neurology, no more than a few words from Critchley's description which was collected from several autopsied cases report and published on the Journal of Brain in 1929[(2)]. After the initial appearance, the diagnosis was denied by most of the modern neurologists even the movement disorder specialists. However, after the inventions of newer generations of Computerized Tomography and the recent high Tesla fielded magnetic resonance image techniques, imaging diagnosis of basal ganglia lesions becomes available. The movement disorder specialists re-examine the idea of vascular contributions to parkinsonism; and, therefore, the concept of vascular parkinsonism is revised. As the aged population increased, more and more evidences had been reported. CNS hemosiderosis is even rarer than vascular parkinsonism. One reason for the rarity is that it is hard to confirm parkinsonism unless the patient was autop-

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Received March 9, 2005. Revised April 8, 2005.
Accepted August 15, 2005.

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sied. Nevertheless, as the development of image techniques especially the gradient-echo MR images, the low signal intensity spots are so obvious to the neuroradiologists that they become a common coincidental finding in daily practice. It is not surprising that we found two such cases in a 6-month period.

Patient 1

A 75-year-old right-handed man was admitted to the hospital because of progressive general rigidity. He was diagnosed as parkinsonism with initial presentations of dizziness, small-stepped gait and bradykinesia in December 1999. Hypertension on anti-hypertensive agents and aortic regurgitation had been noted then. Madopar HBS was tried and his slow movement improved.

He received regular follow-up at our out-patient clinic. But in March 2000, he developed an acute stroke presenting with sudden onset of right side weakness. He recovered gradually with only a mild hemiparesis and was on antiplatelet drugs for stroke prevention. The patient had stopped smoking 30 years earlier, and he stopped drinking alcohol after stroke.

Another stroke happened, in May 2002 presenting with left side limbs weakness. Brain CT revealed suspected lacunar infarction over bilateral basal ganglia, bilateral thalami and right corona radiata. No high density lesion was noted in the above area on brain CT. He still could walk then. In May 2003, urine and stool incontinence occurred and diapers were needed. In June 2003, decreased appetite and progressive bilateral lower leg weakness were observed. Broad-based small-stepped gait, truncal unsteadiness, hyposmia and downward gaze limitation were noted, too. Progressive supranuclear palsy-like presentations were noted, such as vertical gaze limitation which could be overcame by doll-eye maneuver, bradykinesia, small-stepped gait and poor responsiveness to levodopa. No chorea, myoclonus, dystonia, cognitive impairment, nor resting tremor was noted. He was completely bedridden thereafter.

Fever, choking on feeding, violent behavior, visual hallucination, poor digestion, and swallowing difficulty occurred in July 2003. Aspiration pneumonia, hypernatremia and paroxysmal atrial fibrillation were noted.

In August 2003, general rigidity with a progressive course was found. Besides, his head was found to be deviated to the left (as torticollis) and his saliva drooled at the left mouth angle.

Due to repeated stroke episodes and deteriorated clinical course, he was hospitalized for further evaluation in September 2003.

On physical examination, the patient appeared thin and weak. The neck was rigid, tilting to left, but no carotid bruit was heard. Neither goiter nor lymphadenopathy was palpable. The lungs were clear, and the heart sounds revealed regular heart beat without obvious murmur.

On neurologic examination, the patient was alert and oriented; his memory was intact, as was his naming ability. But his response was slow. His speech was hypophonic and slightly dysarthric. No diplopia nor ptosis was noted during the ophthalmologic examination, but slight vertical gaze limitation was found. He could not open his mouth completely. The remaining cranial functions were normal. Muscle power was graded at 4+/4+ throughout, with clinically observable rigidity and spasticity. The sensations of pinprick and vibration were intact. He could not cooperate during the joint position testing due to poor concentration. The finger-to-nose test and the heel-knee-shin test failed due to rigidity and poor response. Gait and Romberg's sign could not be tested because of difficulty in standing. General hyporeflexia was noted but possibly due to inadequate relaxation. The plantar responses were flexor.

T1 and T2-weighted brain MRI in June 2003 (Figs. 1 & 2) revealed multiple hypointensity lesions over pons, thalamus, bilateral corona radiata, bilateral basal ganglia, and bilateral parietal subcortical white matter. Multiple hemosiderin depositions were suspected.

Chronic sub-arachnoid hemorrhage was suspected to cause hemosiderin deposition. Lumbar puncture was performed to detect if any hemorrhage existed. CSF study in September 2003 revealed negative findings except for a low intracranial pressure (opening pressure was 58mmH_2O).

Laboratory data on admission revealed hypercal-

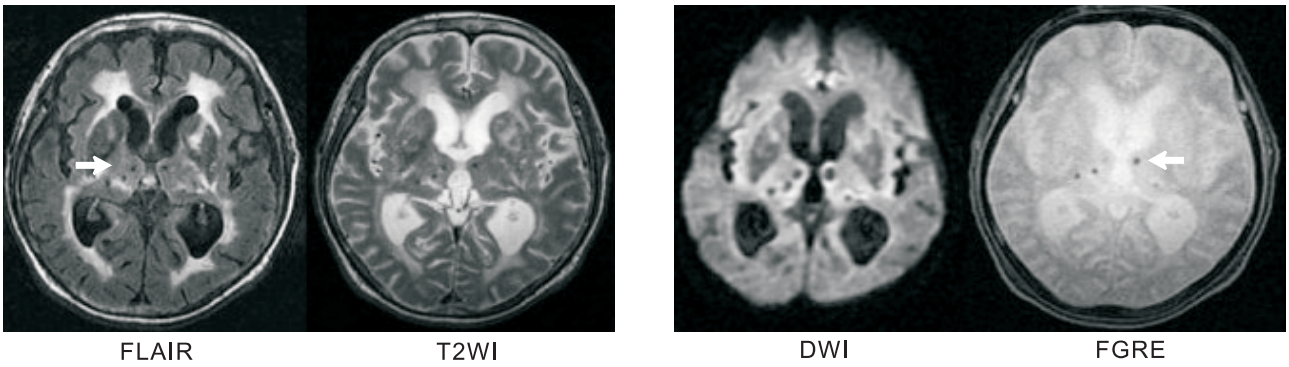

Figure 1. Brain MRI of patient 1 (when PSP-like symptoms occurred)
Multiple hypointense lesions over the bilateral thalami on all pulse sequences (open arrows)
Periventricular hyperintensity on FLAIR image and T2 WI. T2WI: T2-weighted image; FLAIR: fluid-attenuated inversion recovery; DWI: diffusion-weighted image; FGRE: fast gradient echo.

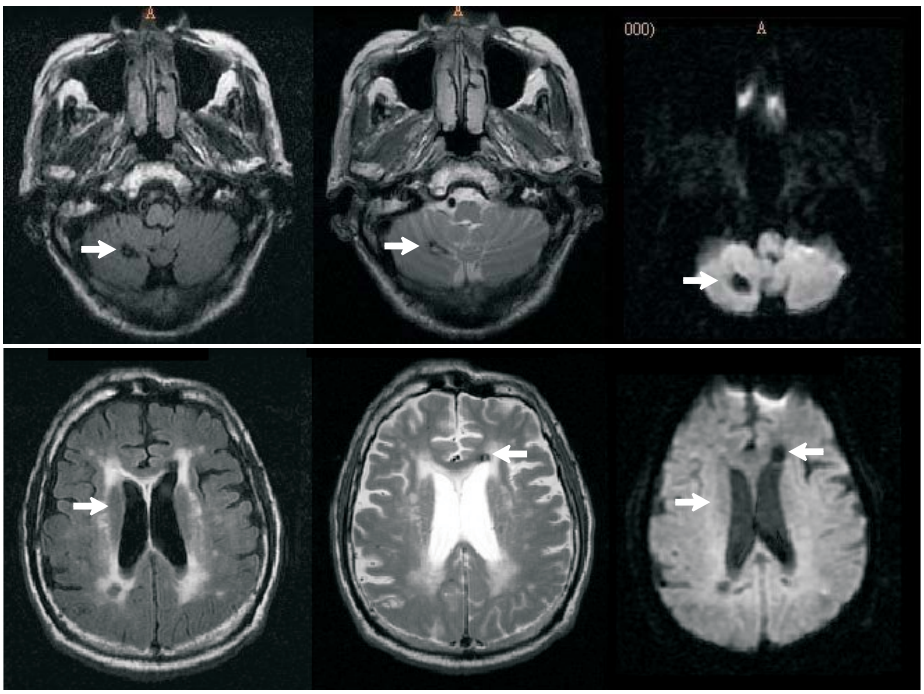

Figure 2. Brain MRI of patient 2 (3 months after the occurrence of gait disturbance)
A profound hypointense lesion with central hyperintensity (open arrows) over the right cerebellar hemisphere. T2WI: T2-weighted image; FLAIR: fluid-attenuated inversion recovery; DWI: diffusion-weighted image.

cemia (serum ion calcium level was 6.36 mg/dl) and elevated ESR (70 mm/hr). Hyper-parathyroidism and hyperthyroidism were suspected. Thyroid and parathyroid function were checked. Hyperthyroidism was found (TSH was less than 0.1 μIU/ml, Free T4 was 5.8 ng/dl).

Tracing back his history, we found that a thyroid disorder was diagnosed when he was in the military service and was treated with anti-thyroid drugs. Besides, several times of rage attack were noted. When he was angry, he sometimes would throw objects toward his wife.

Patient 2

A 80-year-old right-handed male physician was admitted to the hospital because of acute onset of slow

movement, rigid limbs and small-stepped gait since September 2003 with a progressive course.

He suffered from poliomyelitis in his childhood, with the sequela of right leg mild atrophy. Besides, his past history included orbital lymphoma status post radiotherapy and thymoma status post operation. He denied diabetes mellitus or hypertension.

He had difficulty in defecation for about one year. He needed to defecate even more effortfully in recent 3 months, as his wife frequently noticed sweat drops over his forehead after bowel movement, and at the same time he walked and talked slowly. He became very anxious and refused to do anything, which made the patient totally akinetic. Frequent choking on drinking liquid and decreased oral intake made him severely dehydrated.

On physical examination, neither goiter nor lymphadenopathy was palpable. The lungs were clear, and the heart sounds revealed regular heart beat without obvious murmur.

On neurologic examination, the patient was alert and oriented. His response was slow. His speech was hypophonia and slightly dysarthric. Neither diplopia nor ptosis was noted during the ophthalmologic examination, but slight gaze limitation to all directions (primarily vertical direction) was found. Mild left central facial palsy was found. The remaining cranial functions were normal. Muscle power was graded at 4+/4+ throughout, with an increased muscle tone and generalized rigidity. Bilateral hand postural tremor was observed. The sensations of pinprick and vibration were intact. The finger-to-nose test revealed no dysmetria. Gait and Romberg's sign could not be tested because of difficulty in standing. The deep tendon reflexes were decreased generally but this might result from poor relaxation. The plantar response was no response bilaterally.

T1- and T2-weighted brain MRI in December 2003 revealed multiple hypointensity lesions over bilateral hemispheres and right cerebellar peduncle. Multiple hemosiderin depositions were suspected. Besides, old lacunar infarcts over the pons and right corona radiata were noted, too.

Laboratory data on admission revealed no obvious abnormality.

DISCUSSION

In our two reported cases, T1 and T2-weighted brain MRI revealed multiple intracerebral hypointense lesions. Signal-void patterns on both T1 and T2-weighted brain MRI could be fluids with rapid or turbulent flow such as vessels or metal deposition such as calcium, iron and etc[3].

Small amounts of cerebral microbleeding are difficult to detect with T1- and T2-weighted sequences and are best shown on gradient-refocused echo MRI[4]. Signal loss on gradient-echo T2*-weighted MRI may be due to the causes listed in Table 1.

Hemosiderin is a brownish pigment containing iron, so it would present the similar phenomenon on brain MRI. The corresponding lesions on brain CT are not hyperdense. The same lesions were not contrast-enhanced during MRI studies. Cavernous angioma has the typical inhomogenous high signals surrounded by low ring on T2 and T2*-weighted image, which was not shown in the brain images in the first patient. So the possibilities of the lesions to be vessels or calcium deposition were reduced. From this point of view, these multiple signal-void lesions are most likely to be hemosiderin deposition. But the definite diagnosis depends on the brain biopsy. The causes for hemosiderin deposition are hemosiderosis, hemochromatosis, other systemic iron overload, or local hemorrhage such as trauma or vasculitis.

The transferrin saturation levels of our patients were below the normal upper limit and no other systemic manifestations of iron overload such as skin change, hepatomegaly, diabetes mellitus, and etc were noted, which indicated no obvious iron overload. In contrast,

Table 1. *Causes of hypointense lesions on gradient-echo T2*-weighted MRI*

Microangiopathy-related microbleeds[24]
Foci of dense calcification[24]
Occult vascular malformations[24]
Cavernous angiomas[25]
Physiological ferritin[25]
Air in sinuses or mastoid air cells[25]
Some paramagnetic contrast media[25]

low transferrin saturation (11.6%) in our first patient might indicate iron-deficiency. There are few reports of autopsy findings of iron deposition in the brain of patients with hemochromatosis, mainly in the choroid plexus, pituitary gland and in a perivascular distribution. Few cases of iron accumulation in the basal ganglia have been reported[5]. Neuroimaging studies reveal iron deposition in basal ganglia and in the red and dentate nuclei in patients of hereditary ceruloplasmin deficiency with hemosiderosis[6]. Brain images of our patients are not consistent with the findings of haemochromatosis or hereditary ceruloplasmin deficiency with hemosiderosis but are more similar to those of cerebral microhemorrhage, petechial hemorrhage or microbleeds[7].

The causes of cerebral microhemorrhage or microbleeds are atherosclerotic or hypertensive vasculopathies (hypertensive microangiopathy)[8], cerebral amyloid angiopathy[8], hereditary cerebral small vessel disease[9] such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[10], primary angiitis of the central nervous system[11], traumatic microbleeds (Diffuse axonal injury)[12], Binswanger's disease[13], and multiple cavernous angiomas[11]. In the first patient, the cause of cerebral microhemorrhage may be due to hypertensive vasculopathy; in the second patient, the cause may be due to cavernous angiomas.

The risk factors for cerebral microhemorrhage are advancing age[8,14], lacunar infarction[14], white matter changes(leukoaraiosis)[14,15], low serum cholesterol[14,16], a previous stroke history(infarction or hemorrhage)[17], hypertension[17,18], male sex[8], heavy smoker[18], diabetes mellitus[19], and long-term use of antithrombotics[19]. Among these risk factors, hypertension, smoking and diabetes mellitus were the same as the vascular risk factors for stroke listed in Table 2.

Our patients were diagnosed as vascular parkinsonism according to the vascular parkinsonism rating scale listed in Table 2. The first patient had vascular score of 3 which included more than two strokes, two vascular risk factors of stroke(hypertension and smoking) and neuroimaging evidence of vascular disease in two or more vascular territories (bilateral thalami, bilateral corona radiata and etc). The second patient had vascular score of 2 which included neuroimaging evidence of vascular disease in two or more vascular territories (pons and right corona radiata old infarct) and history of two or more strokes (according to the history, step-wise deterioration of gait disturbance may suggest multiple episodes of stroke). Therefore, both our patients could fulfill the diagnosis criteria of vascular parkinsonism.

Pathologically, the lesions most often associated with vascular parkinsonism are the "Binswanger type" of white matter vasculopathy (subcortical white matter lesions) and multiple lacunes affecting the basal ganglia[20]. But the great majority of patients with subcortical ischemic lesions, even if very extensive, do not develop parkinsonism; among patients with cerebrovascular lesions, there is no clear difference in the extent of vascular damage to the basal ganglia and subcortical white matter between patients with and without parkinsonism[20]. Therefore, there is still no clear relationship between vascular lesions and parkinsonism. And the connection between cerebral microbleeds and parkinsonism is also not clarified. Cerebral microbleeds are present in up to 71% of individuals presenting with intrac-

Table 2. *Vascular parkinsonism rating scale [from Winikates and Jankovic1999[26]]*

— Pathologically or angiographically proven diffuse vascular disease	2 points
— Onset of parkinsonism within one month after stroke	1 point
— History of two or more strokes	1 point
— History of two or more vascular risk factors for stroke[1]	1 point
— Neuroimaging evidence of vascular disease in two or more vascular territories	1 point
Vascular parkinsonism = Parkinsonism + Vascular score of 2 or more	

[1] Vascular risk factors for stroke: Hypertension, smoking, diabetes mellitus, hyperlipidemia, presence of heart disease associated with stroke (coronary artery disease, atrial fibrillation, congestive heart failure, valvular heart disease, mitral valve prolapse, or other arrythmias), and other risk factors for stroke (family history of stroke, history of gout, or peripheral vascular disease)

erebral hemorrhage and in 20% to 68% of those admitted with ischemic stroke[8]. Prevalence in healthy clinic-based subjects ranged from 3.1% to 7.7%[8]. And cerebral microbleeds are present in 35% of Chinese patients who were admitted with ischemic stroke[21]. So cerebral microbleeds are not a rare phenomenon. But these data are based on gradient-echo MRI; cerebral microbleeds may not be detected with other sequences of MRI. Because some of the risk factors for vascular parkinsonism and cerebral microbleeds are the same, the combination of parkinsonism and cerebral microbleeds may be more common than we thought.

MR evidence of past microbleeds appears to be a direct marker of increased vascular fragility in patients with various types of small-vessel disease[22]. And microbleeds appear to be a risk factor for subsequent intracerebral hemorrhage among patients with ischemic stroke[21]. Among patients with cerebral microbleeds, more delicate control of vascular risk factors is needed to prevent further vascular events. And the use of antiplatelet and anticoagulant agents in such patients may increase the risk of intracerebral hemorrhage[23].

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