Patterns of chronic venous insufficiency in the dural sinuses and extracranial draining veins and their relationship with white matter hyperintensities for patients with Parkinson's disease

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Background: **Idiopathic Parkinson's disease (IPD) remains one of those neurodegenerative diseases for which the cause remains unknown. Many clinically diagnosed cases of IPD are associated with cerebrovascular disease and white matter hyperintensities (WMHs). The purpose of this study was to investigate the presence of transverse sinus and extracranial venous abnormalities in IPD patients and their relationship with brain WMHs.**

Methods: **Twenty-three IPD patients and 23 age-matched normal controls were recruited in this study. They had conventional neurologic magnetic resonance structural and angiographic scans and, for blood flow, quantification of the extracranial vessels. Venous structures were evaluated with two-dimensional time of flight; flow was evaluated with two-dimensional phase contrast; and WMH volume was quantified with T2-weighted fluid-attenuated inversion recovery. The IPD and normal subjects were classified by both the magnetic resonance time-of-flight and phase contrast images into four categories: (1) complete or local missing transverse sinus and internal jugular veins on the time-of-flight images; (2) low flow in the transverse sinus and stenotic internal jugular veins; (3) reduced flow in the internal jugular veins; and (4) normal flow and no stenosis.**

Results: **Broken into the four categories with categories 1 to 3 combined, a significant difference in the distribution of the IPD patients and normal controls ($\chi^2 = 7.7$; $P < .01$) was observed. Venous abnormalities (categories 1, 2, and 3) were seen in 57% of IPD subjects and in only 30% of controls. In IPD subjects, category type correlated with both flow abnormalities and WMHs.**

Conclusions: **From this preliminary study, we conclude that a major fraction of IPD patients appear to have abnormal venous anatomy and flow on the left side of the brain and neck and that the flow abnormalities appear to correlate with WMH volume. Studies with a larger sample size are still needed to confirm these findings. (J Vasc Surg 2015;61:1511-20.)**

Idiopathic Parkinson's disease (IPD) is the second most common neurodegenerative disease after Alzheimer's disease, and it affects roughly 0.1% to 0.3% of the population.[1] The main known risk factor is age. The etiology of IPD remains unknown. In general, patients with Parkinson's disease (PD) show a loss of dopaminergic neurons in the substantia nigra pars compacta, a reduction of dopamine levels in the striatum over time,[2] and accumulation of intraneuronal inclusions called Lewy bodies and Lewy neurites.[3] Although PD is clinically a motor disorder and has a good response to dopaminergic therapy, in the advanced stages of PD, most of the motor disability symptoms do not respond to dopaminergic therapy anymore.[3] There are also many nonmotor problems, such as cognitive impairment, autonomic dysfunction, neuropsychiatric symptoms,[4] and fatigue,[5] for patients in both early and advanced stages. These findings suggest that the dopaminergic system may not be the only system involved in the PD process.

It has been shown that there is an increased presence of white matter hyperintensity (WMH) in IPD patients.[6] The suggested causes of these deficits include ischemia

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and venous insufficiency from periventricular venular collagenosis.[7-9] WMH might cause or exacerbate motor or cognitive features of PD,[10] especially in the presence of gray matter vascular lesions involving the substantia nigra or striatum,[11] corticostriatal-thalamocortical loop disruption, damage to the interhemispheric connections of the corpus callosum,[10] or disruption of the subcortical afferents. If typical late-onset PD patients have a history of minor stroke, ischemic heart disease, or diabetes mellitus, they show more severe clinical features.[12] One group found that the severity of WMH at baseline was the best predictor of PD progression.[13]

In the last few years, there has been an increasing interest in the role of veins in neurodegenerative diseases,[14] and more attention has been paid to the extracranial veins, such as the internal jugular veins (IJVs) and the azygos veins, as being potential sources of venous hypertension.[14-16] Obstructed venous outflow in the extracranial veins was reported to correlate significantly with hypoperfusion in the brain parenchyma, which could contribute to hypoxia and axonal damage.[17,18] In addition, venous hypertension in the dural sinuses inhibits the absorption of cerebrospinal fluid through arachnoid villi. Some studies showed an association between the venous outflow disturbances with low net cerebrospinal fluid flow in patients with multiple sclerosis (MS).[19,20] An important aspect of the venous abnormalities is that they are potentially treatable with percutaneous transluminal angioplasty (PTA).[21] The first application of PTA in the major cerebral veins was by Zamboni et al[22] in 2009 in MS patients with chronic cerebrospinal venous insufficiency (CCSVI). Since then, a few studies have shown improvement in neurologic outcomes and some quality of life parameters in MS patients who underwent PTA.[22-24]

The use of magnetic resonance angiography and phase contrast flow quantification for the study of the vasculature in patients with PD is a novel concept spurred, in part, by our recent work in MS patients.[25] By the application of flow encoding in the phase contrast sequence, the intensity of the phase images is directly proportional to the speed.[26] The phase intensity in radians is then scaled to velocity by the relationship $v = \text{phase}\ (\text{Venc}/\pi)$, in which Venc stands for velocity encoding. By positioning these two-dimensional (2D) phase contrast magnetic resonance imaging (MRI) flow slices roughly perpendicular to the vessels in the neck, flow in all major vessels can be quantified. Using these morphologic and functional MRI techniques, we can obtain not only the anatomic vascular information but also the quantitative arterial and venous blood flow.

To this end, we proposed this preliminary study with a group of 23 IPD patients to see if some of these patients have abnormal structure or flow either intracranially or extracranially. The outcomes from this study have the potential to open new doors in studying the vascular etiology of IPD.

METHODS

Recruitment of patients and controls

From May 2011 to March 2013, 40 IPD patients were recruited and scanned. Fifteen patients did not receive a complete set of scans because of motion or termination due to the patient's discomfort. Two IPD patients were excluded because they were scanned after taking medication. By excluding those cases, we finally included 23 IPD cases, and for this reason 23 age-matched healthy subjects were included in this study. They were all recruited and imaged at Wuhan Union Hospital, China. The patients with clinically definite IPD were diagnosed by a neurologist at Wuhan Union Hospital on the basis of the United Kingdom PD Society Brain Bank (UKPDSBB) criteria. The patients and controls were imaged under internal review board-approved protocols.

Patients who fulfilled the UKPDSBB criteria were included. However, patients who had any of the following conditions were excluded from this study: any element of the exclusion criteria listed in UKPDSBB; other neurologic disorders, such as Huntington's disease, MS, and normal pressure hydrocephalus; drug-induced parkinsonism; hypoxia; arteriosclerotic disease; and hypertension or diabetes because excessive WMH may show in those patients. The following conditions were excluded for normal controls: history of cardiovascular, neurologic, or psychiatric conditions; head trauma; hypertension; diabetes; and drug or alcohol problems.

All patients and controls consented to be subjects in this study. A 3T Siemens scanner with a 16-channel head/neck coil arrangement was used to acquire the data (Siemens TRIO). Patients underwent conventional clinical imaging as well as angiographic (arterial and venous) and flow quantification imaging. The imaging parameters for each sequence are listed in the Table. The magnetic resonance images of the patients were acquired before medication was taken.

Data processing and analysis

Data processing was done with our in-house software Signal Processing in Nuclear Magnetic Resonance (SPIN, Detroit, Mich). WMHs were evaluated from the 2D fluid-attenuated inversion recovery (FLAIR) images. The total volume of WMH was calculated semiautomatically by SPIN. As the FLAIR data were collected with different resolutions, all the data were normalized to $1 \times 1 \times 5\ \text{mm}^3$ (transverse in-plane) before the volume quantification was done. In addition, the MRI visual rating scale proposed by Scheltens et al[27] was also used for evaluation of the WMH level, which takes the number, size, and location of the WMH into account. The modified visual rating criteria are presented in the Appendix (online only). The 2D time-of-flight (TOF) data were used to evaluate the venous structures in the head and neck. A saturation band was applied to suppress the arterial flow in the 2D TOF images. The maximum intensity projection of the whole series was generated in the coronal view from the 2D TOF coverage. The major veins of interest for the structural analysis included the transverse sinuses and the extracranial veins in the neck.

The phase contrast flow quantification images were used to analyze the through-plane blood flow in the lower neck (C6/C7). Thirty time points were collected for each cardiac cycle. Cardiac gating was achieved by pulse