Angiogenesis

A new paradigm for Parkinson disease with practical and pathogenic implications

David G. Munoz, MD
John M. Woulfe, MD, PhD

Correspondence to Dr. Munoz: munozd@smh.ca

Neurology® 2015;85:1826–1827

The relationship of vascular pathology with Alzheimer disease (AD) is well-established. The clinical expression of a moderate AD load is powerfully modulated by the presence of lacunar infarcts,[1] and midlife hypertension is a risk factor for the development of dementia.[2] On the other hand, Parkinson disease (PD) has been associated with toxins, mitochondrial dysfunction, and impaired degradation of misfolded or abnormally aggregated proteins, but not vascular problems. Until now. As is often the case before a major paradigm-shifting hypothesis is presented—on a grander scale, both relativity theory and the prion hypothesis come to mind—there had been vague rumblings pointing to alteration in the microvasculature in PD. We and others have documented blood–brain barrier (BBB) changes in PD.[3,4] In addition, there are reports of increased capillaries in the substantia nigra,[5] and greater severity of axial motor symptoms in association with white matter lesions (WML),[6] but the article by Janelidze et al.[7] in this issue of *Neurology*® provides a novel perspective with regard to this area of investigation. These authors measured a number of markers of angiogenesis in the CSF in a group of patients with PD—both with and without dementia—and controls, and in 2 validation cohorts, one of them with neuropathologic confirmation of the diagnosis. The proteins investigated relate to the vascular endothelial growth factor (VEGF) family and their receptors, some of which increase, while others decrease, BBB permeability. The data are similar whether all patients with PD or the subgroups with and without dementia are considered, although the threshold for statistical significance is not surpassed in all comparisons. After correcting for age and sex, patients with PD have a distinctive pattern, with higher levels of markers or peptide/receptor ratios increasing BBB permeability, and lower levels of the one (Ang2) that reduces permeability. In patients with PD, these levels correlate with clinical measures of axial impairment, including both objective and subjective assessment of gait, but not with cognitive function. This study must be considered as just the opening salvo, which will have to be replicated by an independent group of investigators. It will be critical to include additional comparison groups, such as other parkinsonisms, Alzheimer disease, and nonparkinsonian patients with orthostatic hypotension.

A possible mechanistic substrate for these findings is provided by the observation that abnormal levels of angiogenic factors were detected exclusively in those patients with PD with coexisting orthostatic hypotension (a credible precursor to transient cerebral ischemia). The second is that BBB permeability (measured as the CSF/blood albumin ratio) correlates with levels of angiogenic factors in PD, but not in controls. The extent of WML did not differ between PD and controls, but correlated with CSF angiogenic factor levels in PD, and not in controls. Microbleeds in patients with PD were also associated with angiogenesis factor levels. The specificity of the findings is bolstered by 2 results: neurofilament light (a marker of neurodegeneration in general) but not tau (an indicator of Alzheimer-related, cortical degeneration) correlated with CSF angiogenesis factors. Neurofilament protein (NFL) also correlated with the extent of WML in PD.

A surprising finding is just how specific these angiogenesis factor levels are: they do not correlate with amyloid levels in CSF or plaque density on histology, nor do they relate to tau levels in CSF or neurofibrillary tangle load on neuropathology.

What drives angiogenesis in PD? The authors provide a credible clue by examining, among other proinflammatory factors, the peptide MCP-1, which covaries with angiogenic factors in PD, but not in controls. These results have both immediate practical and long-term pathogenic implications.

It is possible to propose a mechanistic sequence. A proinflammatory stimulus initiates a cascade that promotes angiogenesis. The subsequent increase in BBB permeability leads to neurodegeneration and—through the same or a different mechanism—to poor control of orthostatic blood pressure. The transient cerebral ischemia thus produced leads to WML, which results in impaired axial motor control,

See page 1834

From the Neuroscience Research Program (D.G.M.), The Keenan Research Centre of the Li Ka Shing Knowledge Institute and Department of Laboratory Medicine, St. Michael's Hospital; the Department of Laboratory Medicine and Pathobiology (D.G.M.), University of Toronto; the Centre for Cancer Therapeutics (J.M.W.), Ottawa Hospital Research Institute; and the Departments of Pathology and Laboratory Medicine (J.M.W.) and Biochemistry, Microbiology and Immunology (J.M.W.), University of Ottawa, Canada.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

prominently affecting gait. Increased CSF NFL mirrors this development. The findings reported here suggest that this process affects only a subset of patients with PD, and occurs early, since there is no correlation with duration of disease. The identification of this subset—possibly by its association with orthostatic hypotension and WML—has implications for immediate action (since Food and Drug Administration–approved treatments exist)[8] as well as for future therapeutic developments.

From the point of view of pathogenesis, the study raises the question of what triggers the inflammation that drives the process. There is no shortage of answers. For example, we have speculated that Epstein-Barr virus may be involved[9] and that the appendix may be a site where the inflammatory process develops,[10] but other sound hypotheses have also been proposed.[11]

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

D.G. Munoz has participated with one of the authors of the study (Dr. Beach) in a multicenter research grant unrelated to this article. J.M. Woulfe reports no disclosures relevant to the article. Go to Neurology.org for full disclosures.

REFERENCES

1. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease: The Nun Study. JAMA 1997;227:813–817.
2. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol 2011;7:137–152.
3. Gray MT, Woulfe JM. Striatal blood-brain barrier permeability in Parkinson's disease. J Cereb Blood Flow Metab 2015;35:747–750.
4. Kortekaas R, Leenders KL, van Oostrom JC, et al. Blood-brain barrier dysfunction in parkinsonian midbrain in vivo. Ann Neurol 2005;57:176–179.
5. Faucheux BA, Bonnet AM, Agid Y, Hirsch EC. Blood vessels change in the mesencephalon of patients with Parkinson's disease. Lancet 1999;353:981–982.
6. Bohnen NI, Albin RL. White matter lesions in Parkinson disease. Nat Rev Neurol 2011;7:229–236.
7. Janelidze S, Lindqvist D, Francardo V, et al. Increased CSF biomarkers of angiogenesis in Parkinson disease. Neurology 2015;85:1834–1842.
8. Biaggioni I. New developments in the management of neurogenic orthostatic hypotension. Curr Cardiol Rep 2014;16:542.
9. Woulfe JM, Gray MT, Gray DA, Munoz DG, Middeldorp JM. Hypothesis: a role for EBV-induced molecular mimicry in Parkinson's disease. Parkinsonism Relat Disord 2014;20:685–694.
10. Gray MT, Munoz DG, Gray DA, Schlossmacher MG, Woulfe JM. Alpha-synuclein in the appendiceal mucosa of neurologically intact subjects. Mov Disord 2014;29:991–998.
11. Dobbs SM, Dobbs RJ, Weller C, et al. Peripheral aetiopathogenic drivers and mediators of Parkinson's disease and co-morbidities: role of gastrointestinal microbiota. J Neurovirol Epub 2015 Jun 20.