Ischemic brain injury in hemodialysis patients: which is more dangerous, hypertension or intradialytic hypotension?

Christopher W. McIntyre[1] and David J. Goldsmith[2]

[1]Division of Nephrology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada and [2]Guy's and St. Thomas' NHS Foundation Trust, King's College Academic Health Partners, London, UK

Abnormalities of cognitive function and high levels of depression incidence are characteristic of hemodialysis patients. Although previously attributed to the humoral effects of uremia, it is becoming increasingly appreciated that many elements of the overall disease state in CKD patients contribute to functional disturbances and physical brain injury. These factors range from those associated with the underlying primary diseases (cardiovascular, diabetes etc.) to those specifically associated with the requirement for dialysis (including consequences of the hemodialysis process itself). They are, however, predominantly ischemic threats to the integrity of brain tissue. These evolving insights are starting to allow nephrologists to appreciate the potential biological basis of dependency and depression in our patients, as well as develop and test new therapeutic approaches to this increasingly prevalent and important issue. This review aims to summarize the current understanding of brain injury in this setting, as well as examine recent advances being made in the modification of dialysis-associated brain injury.

Kidney International advance online publication, 8 April 2015; doi:10.1038/ki.2015.62

KEYWORDS: brain injury; hemodialysis; leukoaraiosis; myocardial stunning; stroke

Correspondence: *Christopher W. McIntyre, Division of Nephrology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Lilibeth Caberto Kidney Clinical Research Unit, Room ELL-101, London Health Sciences Centre 800 Commissioners Rd E, Ontario N6A5W9, Canada. E-mail: cmcint48@uwo.ca*

Received 20 June 2014; revised 5 November 2014; accepted 11 December 2014

Chronic kidney disease (CKD) patients are subject to a wide variety of pathophysiological processes that challenge the structural and functional integrity of the central nervous system. Neurological dysfunction in general in this patient group can be episodic or chronic and reflect an equally wide range of humoral, metabolic, inflammatory, and vascular insults. Our understanding of brain structure in patients receiving hemodialysis (HD) has evolved in tandem with advances in neuroimaging. Progression from early computed tomography-based studies to magnetic resonance imaging (MRI), high-field MRI, and now dynamic assessment of perfusion and ultrastructure by a variety of more recently developed MRI techniques has allowed increasing appreciation of the scope and scale of brain injury in HD patients.

There are multiple pathologies that have been described by brain MRI appearances in dialysis patients. These may be entirely asymptomatic or linked to more subtle defects in neurocognitive function, often only apparent on specific testing.[1] Many of the same processes drive this entire spectrum and are often progressive. Many of these changes do not appear to be strongly associated with classical cardiovascular risk factors and instead seem to be predominantly driven by other factors, such as microvascular disease, inflammation, and challenged perfusion (both in general and/or episodically during HD treatment itself). These abnormalities range from classic stroke to silent cerebral infarct (SCI) and more subtle changes both in the white matter (leukoaraiosis) and gray matter (cortical atrophy). In this way, the situation with cardiac injury on dialysis is mirrored —with more non-ST elevated myocardial infarctions than classical completed transmural myocardial infarctions.

Many of these processes reflect continued influence of the underlying disease states responsible for the dialysis requiring CKD. Superimposed on the pathophysiology already familiar from the study of an aging and increasingly vascularly challenged population, additional systemic cardiovascular structural and functional progressive abnormalities (resulting directly from the chronic uremic state) predispose the brain to further injury.

There is strong emerging evidence that the HD procedure itself causes significant systemic circulatory stress.[2] This

circulatory stress interacts with complex hemodynamic factors causing perfusion anomalies that accelerate end-organ damage in a wide range of vulnerable vascular beds.[3] Initially, this work focused on the heart, but emerging evidence strongly suggests that a much wider range of organs are affected. These include the gut, kidney, skin, and, critically, the brain.[1]

Cognitive decline in patients with renal disease seems to develop with the progression of CKD, even before starting HD.[4] However, it is becoming more evident that HD patients exhibit greater levels of functional and cognitive deficits. The initiation of HD is associated with a sharp deterioration in functional status, measured by activities of daily living scores.[5] This decline in functional status is proportionally linked to higher mortality rates in this population.[5] Accelerated brain injury in HD patients appears to be functionally significant, both with reduced neurocognitive performance and potentially as a biological basis for increasing depression[6] and social dependency. This article aims to review the development and functional consequences of progressive brain injury in HD patients, and to explore the spectrum of structural changes seen and the interaction between this injury, cardiovascular status, and dialysis treatment itself.

SPECTRUM OF STRUCTURAL BRAIN INJURY IN HD PATIENTS

Cerebrovascular disease in dialysis patients is prevalent and is a major cause of morbidity in this group.[7] It has been reported that patients with end-stage renal failure are at a 3–9 times higher risk of hospitalization with stroke compared with the general population.[8] The etiology of cerebrovascular disease in patients with end-stage renal disease, whether or not on HD, is poorly understood and is multifactorial.

There are several pathologies described based on the brain MRI appearance of dialysis patients. The first is SCI, as described in multiple studies.[9] SCI was defined in those studies as areas that are >5 mm with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. The second described pathology is generalized cerebral atrophy and finally leukoaraiotic white matter changes.

SCIs

Nakatani *et al.*[9] examined the hypothesis that HD patients develop SCIs. These silent infarcts are mainly subcortical and lacunar without causing any neurological deficit, but they are thought to be a risk factor for developing symptomatic infarct or hemorrhagic strokes. They compared 123 HD patients with 53 normal individuals and found that the incidence of SCI was much higher in the HD group. Among the 60 HD patients who developed SCI, 57 had lacunar infarcts. However, when performing multiple logistic regression analysis, they found that hypertension and dyslipidemia were not independent risk factors for developing SCI in this patient group (in contrast to the general population). Anan *et al.*[10] examined a group of 50 HD patients and found that in those who developed SCI a simple logistic regression analysis identified smoking, lower HDL-C, higher uric acid levels, and higher levels of hepatocyte growth factor as risk factors. Furthermore, cardiac evaluation using echocardiography revealed that the group that developed SCI exhibited higher interventricular septal thickness, higher posterior wall thickness, and higher left ventricular mass index. There was no difference in the left ventricular ejection fraction between the two groups. Finally, 24-h blood pressure monitoring identified that the group that developed SCI lacked the nocturnal fall in blood pressure. Similarly, Anan *et al.*[11] observed 77 HD patients and found again that smoking, lower HDL-C, and higher uric acid levels were risk factors for developing SCI. They also associated higher levels of high-sensitivity C-reactive protein with SCI. These findings reinforced the importance of systemic cardiovascular structure and performance to the brain in this setting.

Cerebral atrophy

Kamata *et al.*[12] compared the computed tomography brain images of 56 HD patients with 42 controls and found that the brain atrophy index (a semiquantitative measure using visual rating scale of T (1)-weighted MRI images) was greater in the HD group. Prohovnik *et al.* studied the physiological changes in the cerebral circulation during HD. They used quantitative MRI to measure cerebral atrophy, MRI measurements of regional cerebral blood flow, quantitative Doppler measurements of blood flow in internal carotid artery, and measurement of oxygen saturation in the frontal cortex in a small group comprising 10 HD patients and 5 peritoneal dialysis (PD) patients and compared them with 5 controls without CKD.[13] The key finding was that cerebral atrophy was more prevalent in HD patients, and global reduction in the gray matter strongly correlated to dialysis vintage (Figure 1).

Leukoaraiosis

Leukoaraiosis describes changes in the brain white matter caused by loss of axons and myelin owing to ischemic injury. The MRI appearance is that of high signal intensity on T2-weighted images. Leukoaraiosis has been described as a risk factor developing dementia, mobility problems, and strokes[14,15] and is mainly described in the literature as age related. Kim *et al.*[16] compared a group of 57 PD patients with a non-CKD control group and found a higher incidence of leukoaraiosis in the PD group. Although the study by Kim *et al.*[16] is the only study that used the specific term leukoaraiosis in dialysis patient, it is possible that on the basis of its definition Nakatani *et al.*[9] and Anan *et al.*[11] described the same pathology as with the diagnosis of SCI. The limitations of the imaging used in these studies would allow for significant diagnostic overlap.

Recently, using more advanced brain imaging (brain diffusion tensor imaging), these lesions have been demonstrated to be a universal finding in HD patients, after only 3 months of dialysis.[17] The severity of reduction in cognitive function was proportional to the distribution and amount of