Effects of Hyperphosphatemia on Cerebral Small Vessel Diseases in Chronic Kidney Disease

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Objectives: Chronic kidney disease (CKD) has been recently identified as a significant risk factor for stroke as well as for subclinical vascular diseases such as cerebral small-vessel diseases (CSVD). Endothelial dysfunction is a major contributor to CSVD in CKD. Interestingly, both kidney and cerebral microvasculature share similar anatomical and physiologic characteristics. The goal of this study was to elucidate the effects of hyperphosphatemia in cerebral microvasculature using human brain microvascular endothelial cells (HBMECs) and CKD mice as our models.

Methods:
CKD mice model was generated by 5/6 nephrectomy on 8-week-old C57BL/6 mice. Mice were sacrificed at four months after 5/6 nephrectomy. β-glycerolphosphate disodium (2mM, 5mM) was used in HBMECs for 72 hours, in vitro.

Results:
Our results showed that CKD mice had decreased myelinated nerve fibers in the corpus callosum and cerebral cortex and loosening myelinated fibers in the corpus callosum. We found collagen IV accumulation in brain microvasculature, a pattern associated with aging.. Serum phosphate levels were significant increased in CKD mice compared to control mice. In HBMECs, β-glycerolphosphate disodium decreased cell viability and increased caspase-3 mediated apoptosis. In addition, Collagen IV expression increased in a dose-dependent manner at 72 hours after β-glycerolphosphate disodium treated HBMECs.

Conclusion:
Our data show for the first time that cerebral white matter and microvascular dysfunction occurs in uremic environments in CKD, in vitro and in vivo. Furthermore, CSVD can be driven in part, by CKD induced hyperphosphatemia. Our data provides a potential mechanism for the development of CSVD in CKD patients.