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Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by over-active parathyroid gland(s) and elevated blood calcium levels. Although 80% of PHPT patients are said to be “asymptomatic” (i.e. lacking the classical manifestations of nephrolithiasis and osteitis fibrosa cystica), this term is a misnomer because most patients report neuropsychological symptoms, including reduced memory and concentration. Although both hypercalcemia and elevated parathyroid hormone (PTH) could have cognitive effects, the mechanism of cognitive dysfunction in PHPT has never been delineated. Most studies do indicate neuropsychological sequelae of PHPT but reversibility after parathyroidectomy (PTX) has been inconsistent across investigations. These inconsistencies may be related to small sample sizes in some studies and variability in the aspects of cognition examined. Because of such limitations, patients with cognitive symptoms are still deemed “asymptomatic” and cognitive dysfunction is not currently an indication for PTX. This remains the biggest unresolved issue in the management of asymptomatic PHPT. Recently, we made progress in this challenging area by showing with validated tools that specific cognitive dysfunction is present in PHPT and improves after surgical cure. A potential vascular mechanism is suggested by our work demonstrating increased aortic and carotid vascular stiffness in PHPT in association with extent of PTH elevation. Our new preliminary data supports the presence of similar PTH-dependent changes in the intracerebral vasculature that may underlie cognitive impairment in PHPT. There is support for this concept from work showing that cerebral hemodynamic dysfunction is associated with cognitive impairment in vascular dementia and carotid disease. Moreover, a recent epidemiological study found elevated PTH to be a risk factor for cognitive decline in older adults. The proposed studies are intended to determine if the above PTH-dependent vascular mechanism is responsible for cognitive dysfunction in PHPT, whether the process is attributable to PTH and reversible with cure of PHPT, and which brain regions are affected. First, we will use transcranial Doppler to confirm that intracerebral vasomotor reactivity (VMR) is reduced in PHPT, and associated with elevated PTH (but not calcium) and cognitive changes. Second, we will determine if impaired VMR is reversible with PTX. Finally, we will identify the sites in the brain affected by PHPT using functional magnetic resonance imaging. The data from these studies will address a research goal of the 4th International Conference on Asymptomatic PHPT (2013), which highlighted the need for data regarding the cognitive effects of PHPT. Ultimately this information may lead to alteration of surgical guidelines for PHPT patients. Further, if our hypothesis regarding PTH-dependent changes in cerebral vascular function and cognition is confirmed, these data would have implications for a much broader and larger group of patients with PTH excess, including those with secondary hyperparathyroidism from vitamin D deficiency, kidney disease and other disorders.