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Highlights in clinical autonomic neurosciences: Brain volume and autonomic regulation

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ABSTRACT

Advances in volumetric magnetic resonance imaging (MRI) technology are beginning to provide structural correlates to functional dysautonomic syndromes in the brain. This paper highlights several interesting recent discoveries in which measurable variations in general or regional subcortical or cortical brain volume corresponded to changes in blood pressure or heart rate. Although these MRI findings currently lack diagnostic value in routine clinical practice, they may provide important clues to the pathophysiology of autonomic disorders and to links between autonomic and cognitive disorders. If validated by further studies, they also have potential implications for the management of orthostatic hypotension, particularly when combined with hypertension.

Introduction

Specific brain regions modulate cardiovascular autonomic control. The nucleus tractus solitarius and ventrolateral medulla, which mediate baroreflex oversight of dynamic changes in blood pressure, connect with the hypothalamus, medial prefrontal cortex and insular cortex, which together influence cardiovascular function (Verberne and Owens, 1998; Nagai et al., 2010; Beissner et al., 2013). This central autonomic network, which was initially mapped out in animals through anatomic and physiologic studies, has been confirmed (Henderson et al., 2012) and can now be studied in humans through noninvasive neuroimaging combined with physiologic studies.

Kim, J.B., Suh, S.-i, Seo, W.-K., et al. (Seoul, Republic of Korea). 2014. Right insular atrophy in neurocardiogenic syncope: a volumetric MRI study. AJNR Am J Neuroradiol 35, 113–118.

Article Summary

These investigators applied voxel-based morphometry of 3 T MR brain images to compare regional gray matter volumes in 32 patients with recurrent neurally mediated syncope to those in an equal number of controls. The patients were age 24.1 ± 6.9 and 34% male. The diagnosis was confirmed by tilt table testing, which was defined as positive when patients developed their typical symptoms of spontaneous syncope in association with hypotension, bradycardia, or both. The volumetry in each hemisphere focused on three cortical regions (the rostral and caudal anterior cingulate and insula) and one subcortical region (the amygdala) involved in cardiovascular autonomic modulation.

The study found that patients with recurrent neurally mediated syncope had regional atrophy involving the right insular cortex (7323 ± 689.1 versus 8011 ± 932.5 mm^3, $p = 0.002$). Regression analysis showed further that smaller right insular volumes correlated with larger drops in both systolic ($r = -0.410$, $p = 0.020$) and diastolic ($r = -0.507$, $p = 0.003$) pressures in patients who had a vasodepressor response during tilt table testing.

Commentary

The pathophysiologic mechanisms of neurally mediated syncope (neurocardiogenic syncope) remain incompletely elucidated. Prevailing theory holds that syncope results from transient failure of the brain to communicate the appropriate autonomic signals to the cardiovascular system to maintain blood pressure, often in response to orthostatic or other stress, resulting in a transient drop in blood pressure that decreases cerebral blood flow to a level sufficient to impair consciousness (Freeman et al., 2011). This study may be the first to establish a

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structural basis in the brain for what has long been considered to be a functional dysautonomia.

Since the images captured the insular cortices of these patients at only one moment in time, they do not establish a causal relationship. Right insular cortex atrophy might provide the neurological substrate for an increased risk of syncope, analogous to the hippocampal sclerosis that underlies some cases of epilepsy. Alternatively, repeated episodes of cerebral hypoperfusion or the neural response to it might somehow cause right insular atrophy. This ambiguity might be resolved by prospective studies following insular volume over time in patients with syncope. Whether insular volume returns to normal once syncopal episodes cease recurring would be a further question worth exploring.

Beauchet, O., Celle, S., Roche, F., et al. (Angers Cedex, France). 2013. Blood pressure levels and brain volume reduction: a systematic review and meta-analysis. Journal of Hypertension 31, 1502–1516.

Article Summary

A systemic review and meta-analysis of the literature sought to correlate blood pressure levels with reduction in brain volume, with particular attention to the hippocampus, since previous studies have shown hypertension to be a risk factor for Alzheimer's disease, a pathological signature of which is hippocampal atrophy. Of 609 screened abstracts, 28 studies were selected in which brain volume reduction as measured by MRI and blood pressure were outcomes.

Nearly all (92.9%) of the studies showed a significant association of higher blood pressure levels with total or regional brain volume reduction. Notably, blood pressure-related brain volume reduction preferentially affected the prefrontal cortex and hippocampus.

Commentary

This study provides persuasive evidence that high blood pressure levels are associated with reduction of brain volume, specifically in the prefrontal cortex and hippocampus. This phenomenon appears to be specific to gray matter (Celle et al., 2012).

Despite the superficial simplicity of measurements of blood pressure and brain volume, the authors acknowledge that rigorous studies correlating the two are methodologically challenging. These variables are temporally dynamic, changing with age, with medication adjustments, and in response to many factors. Large studies cannot easily control for antihypertensive medications. Whether correlations indicate cause or effect may be uncertain. Previous literature has yielded conflicting results in regard to whether high systolic or diastolic blood pressure levels are more closely linked to brain atrophy and whether the age of onset of hypertension plays a role (Qiu et al., 2005).

Many further questions remain to be explored, such as the possible cerebral and future cognitive implications not only of nocturnal nondipping (Hajjar et al., 2010) but also of recumbent hypertension in patients with baroreflex failure and transient forms of severe hypertension in patients with autonomic storms.

In comparison to research on hypertension, less attention has focused on the relationship between hypotension and brain volume, which may also be pertinent to the role of blood pressure in neurodegeneration. If high blood pressure is detrimental to brain volume, might blood pressure at the low end of normal, either early or late in life, at baseline or orthostatic, in any way be protective? Other studies to date have shown mixed results. In patients with atherosclerosis, lower systolic blood pressure and lower pulse pressure increased the risk for cortical atrophy (Muller et al., 2010), while in another study cortical volume changes were unrelated to orthostatic hypotension (Colloby et al., 2011). These disparities suggest a complex relationship of blood pressure to brain volume.

Jochemsen, H.M., Muller, M., Visseren, F.L., et al. (Utrecht, the Netherlands) 2013. Blood pressure and progression of brain atrophy: the SMART-MR study. JAMA Neurol 70, 1046–1053.

Article Summary

In a prospective cohort study of 663 patients of mean age 57 ± 9 years with manifest atherosclerosis, the investigators correlated blood pressure with brain total gray matter over time using multivariable adjusted regression analysis. Blood pressure was measured by sphygmomanometry at baseline in a seated position and again at a mean of 3.9 years of follow-up. Gray matter volume at both time points was determined by an automated segmentation MRI protocol, which analyzes T1-weighted gradient-echo inversion recovery and FLAIR sequences to calculate ventricular volume as an inverse indicator of global subcortical brain atrophy. Regional differences in brain volume were not examined.

They reported two findings. First, patients with lower baseline diastolic blood pressure showed greater progression of subcortical, but not gray matter or parenchymal, atrophy. Secondly, in patients with higher baseline blood pressure, declining diastolic and, to a lesser extent, systolic blood pressure levels over time showed less progression of subcortical brain atrophy. On this basis they hypothesized that low diastolic blood pressure might be a risk indicator of early vascular aging or stiffness and that further blood pressure lowering in the low baseline group might be harmful.

Commentary

To put these findings in perspective, it is helpful to consider how small were the magnitude of the changes the investigators recorded. The change in subcortical volume was 0.2% ± 0.3%, and the change in diastolic blood pressure was just 0.07% ± 0.06%. Whether a change in blood pressure of less than one-tenth of one mm Hg is clinically meaningful is uncertain.

Glodzik, L., Rusinek, H., Pirraglia, E., et al. (New York, N.Y., U.S.A.) 2014. Blood pressure decrease correlates with tau pathology and memory decline in hypertensive elderly. Neurobiology of Aging 35, 64–71.

Article Summary

This study examined whether longitudinal reduction in mean arterial pressure in 77 patients was related to reduction in hippocampal volume, changes in neuropsychological scores or cerebrospinal fluid biomarkers of Alzheimer's disease. Patients' mean age was 63.4 years, and 24 had hypertension. The investigators found no relationship between blood pressure and hippocampal volume at baseline or at followup 2 ± 0.5 years later. Longitudinal decrease in mean arterial pressure was, however, related to decline in verbal episodic memory ($\beta = 0.50$, $p = 0.01$) and increased p-tau$_{181}$ ($\beta = -0.50$, $p = 0.01$), but only in the patients with hypertension. The investigators postulated that in hypertensive patients reduction in mean arterial pressure might lead to cerebral hypoperfusion, accumulation of hippocampal neurofibrillary pathology, and cognitive decline, even before hippocampal atrophy could be detected.