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Huntington's disease is a rare autosomal dominant neurodegenerative disease caused by cytosine-adenine-guanine (CAG) trinucleotide expansion of the huntingtin gene on chromosome 4p. Primarily a disease of the central nervous system with accumulation of the huntingtin protein within the cellular nucleus and cytoplasm, the neuronal loss is predominantly located in the caudate and putamen of the basal ganglia. The basal ganglia consist of a group of structures including the globus pallidus, substantia nigra and subthalamic nucleus. Functionally, they are collectively involved in movement, cognition, and emotion. As such, Huntington's disease is a clinical triad of motor dysfunction (i.e., chorea), cognitive impairment and psychiatric disturbances.

In the last decade, it is increasingly recognized that various neurodegenerative disorders including Huntington's disease can have associated autonomic dysfunction. For example, spinocerebellar ataxias type 2 is also an autosomal dominant disease due to CAG repeat expansion in the ATXN2 gene on chromosome 12q. Similar to Huntington's disease, symptoms of spinocerebellar ataxias type 2 also include ataxia, chorea, dementia and autonomic dysfunction.[1] In these patients, ^{123}I-metaiodobenzylguanidine (MIBG) scans showed loss of post-ganglionic myocardial sympathetic nerve fibers with significantly lower early and late heart-to-mediastinum (H/M) ratios compared to controls.[2] Similarly, diseases such as Parkinson's disease and Lewy body dementia (the second most common type of dementia after Alzheimer's) ''resembles'' Huntington's disease as they are also characterized by disturbances in sleep, behavior, cognition, movement and autonomic function. These patients are known to have autonomic dysfunction and abnormal MIBG scans compared to normal controls.[3,4]

There is a strong body of evidence indicating that the autonomic nervous system plays an important role in the genesis of sudden cardiac death.[5,6] Increased cardiac sympathetic activity without opposing increase in parasympathetic vagal activity can promote ventricular arrhythmias by reducing the ventricular refractory period and ventricular fibrillation threshold, promote triggered activity after potentials, and enhance cardiac automaticity with accelerated generation of action potential in abnormal tissue. Traditionally, autonomic function was frequently assessed by means of heart rate variability (HRV) analysis. Several studies to date have shown increased sympathetic and reduced parasympathetic vagal activities in patients at middle stages of Huntington's disease, as well as in pre-symptomatic mutation carriers.[7] However, HRV is influenced by age, race, gender, cardiovascular fitness, sleep/wake cycles and drug treatment. In addition, it is only interpretable in patients with predominantly sinus rhythm and have accurate R-wave detection. Ultimately, HRV is an indirect assessment of the autonomic nervous system and does not directly measure absolute sympathetic and parasympathetic activity. In contrast, MIBG scans can directly quantify cardiac sympathetic innervation and

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tone.[2,4] The calculated early H/M ratio is considered to reflect the density of the cardiac sympathetic nerve endings, the washout rate (WR) an indicator of the cardiac sympathetic tone, and the late H/M ratio reflects both.

In the present study by Assantea et al. published in this issue of the Journal, the authors were first to performed MIBG scans in 15 patients at early and middle stages of Huntington's disease and 10 controls.[10] Clinical symptoms of autonomic dysfunction in various domains (e.g., cardiovascular, gastrointestinal, urinary, etc.) were also evaluated by means of Scales for Outcomes in Parkinson's disease-autonomic symptoms (SCOPA-AUT) questionnaire. As expected, the degree of CAG expansion was directly correlated with the age of disease onset. However, there were several interesting findings in the study. First, there were no differences in early H/M ratio, late H/M ratio, and WR between Huntington's disease patients vs. controls. Secondly, a higher SCOPA-AUT score (i.e., more symptoms of autonomic dysfunction) was correlated with disease duration and WR, but was not correlated with early or late H/M ratio. Together, these findings suggested that cardiac sympathetic tone is altered in patients with Huntington's disease, but the overall density of sympathetic nerve endings in the myocardium may be preserved in patients with early and middle stage disease. As such, this study potentially lends weight to recent observations that higher brain centers may exert a direct influence on the autonomic nervous system.

Current anatomical teaching states that the sympathetic nervous system consists of the pre-ganglionic neuron arising from the thoracolumbar (T1 to L1-L2) spinal cord, travels to a ganglion, synapses with the post-ganglionic neuron, and then extends to the rest of the body. In the heart, the left stellate ganglion and left sympathetic chain are thought to predominantly supply the left ventricle and is involved in cardiac rhythm/arrhythmia. However, recent studies suggest that cardiac autonomic regulation may be directly under cortical and subcortical control, specifically the prefrontal cortex, bilateral insular cortex, anterior cingulate gyrus, amygdala, and hypothalamus.[11,12] Further indirect evidence from stroke patients with involvement of the left and right insular cortices have clinical features of cardiac autonomic dysfunction, arrhythmias and increased risk of sudden death.[13,14] Interestingly, although anatomical and functional neuroimaging of patients with Huntington's disease have long shown atrophy and metabolic changes in the caudate nucleus[15], recent study suggested that patients may also have neurodegeneration in the insular cortex and amygdala.[16] Therefore, this may be the mechanism for the autonomic dysfunction in patients in early and middle stages of Huntington's disease.

However, there are still several significant limitations in the present study. First, the number of patients was extremely small, and the study results will need to be corroborated in other larger studies. Secondly, we do not know if patients with more advanced disease have preserved or reduced myocardial sympathetic innervation. Thirdly, the spatial resolution of MIBG is limited and positron emission tomography imaging using ^{11}C-hydroxyephedrine may provide better differentiation between innervated and denervated myocardium, and is superior in evaluating neuronal heterogeneity.[17] Fourthly, current tracers only allows evaluation of cardiac sympathetic innervation and tone, whereas direct imaging of the parasympathetic system is more limited. Finally, the SCOPA-AUT score was originally developed for assessing symptoms of autonomic dysfunction in patients with Parkinson's disease. Although the questionnaire have since been clinically used in patients with Huntington's disease, the score was never validated against objective measures of autonomic function.[18]

Ultimately, more research is clearly needed to further our understanding of the pathophysiology and role of autonomic dysfunction in this rare but disabling and fatal disease. The present study has provided valuable insights into the complex interactions between the heart, brain, and autonomic nervous system. Understanding the factors that control cardiac autonomic function may permit identification of potential therapeutic strategies to prevent sudden cardiac death.

Disclosures

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