Let's not forget about the vagus and other updates on recent autonomic research

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Does alpha-synuclein spread through the vagus nerve?

Autonomic failure is a prominent feature of synucleinopathies such as Parkinson disease (PD), dementia with Lewy bodies, multiple system atrophy, and pure autonomic failure (PAF). In these conditions, misfolded alpha-synuclein accumulates in neuronal cells and eventually leads to cell death. Misfolded alpha-synuclein can also spread from cell to cell in prion-like fashion [1], and researchers have demonstrated in animal models that misfolded alpha-synuclein can spread from the gastrointestinal system to the brainstem via the vagus nerve. In support of this hypothesis, resection of the vagus nerve in animals seems to halt the progression of alpha-synuclein spread [2]. Taken together, these findings raise the possibility of the vagus nerve as a key pathway for alpha-synuclein progression from the gastrointestinal system to the central nervous system in humans. While a prospective study of vagus nerve transection in humans might not be feasible due to ethical reasons, several groups have examined this connection by retrospectively evaluating patients who had already undergone vagotomy for other conditions. Although not routinely performed currently, vagotomies were a relatively common procedure for the treatment of peptic ulcer disease several decades ago.

In a recent article published in *Neurology* [3], using a Swedish patient registry, researchers analyzed the incidence

of PD in a group of subjects who underwent vagotomy surgery. They identified 9430 patients who had vagotomies during the study period and matched them with 37,200 controls. A total of 4930 cases of PD were reported during the follow-up, with an incidence rate of 61.8 per 100,000 person-years, compared to 67.5 per 100,000 person-years in the control group. While the difference between both groups was not statistically significant, patients who had total vagotomy (unlike selective vagotomy) seemed to have a mild protective effect (hazard ratio 0.54, 95% CI 0.32–0.91).

A similar study [4], published in 2015 in *Annals of Neurology*, analyzed data from a Danish registry and suggested that truncal vagotomy had a mild, but not statistically significant, benefit in preventing PD; again there was no benefit from selective vagotomy in this cohort. These studies raise many interesting questions. With researchers looking for mechanisms that can halt the rostro-caudal migration of abnormal alpha-synuclein, it is tempting to hypothesize that vagal nerve manipulation might be an option for prodromal patients who are genetically predisposed to PD. As we try to understand the factors predicting conversion of PAF to other alpha-synucleinopathies, what role, if any, does vagotomy have? Certainly, the data does not yet support this invasive procedure for this indication, and the spread of alpha-synuclein along peripheral autonomic nerves is still poorly understood; however, future studies should not forget about the vagus as a potential target for neuroprotection.

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Vagus nerve stimulation for refractory epilepsy: why does heart rate matter?

Heart rate variability (HRV) offers many insights into autonomic cardiac responsiveness, and is often referenced in the literature as a noninvasive measure of overall

autonomic health. HRV is modulated in large part by the vagus nerve, in concert with sympathetic adrenergic inputs and cardiorespiratory chemo- and mechanoreceptors. Vagus nerve stimulation (VNS) involves implantation of an electrical stimulator with leads in the left vagus nerve—the left is chosen because the right vagus exerts greater cardiac influence, hence, the potential for stimulus-induced arrhythmias. VNS has been approved for several conditions, including refractory epilepsy, depression and various chronic pain syndromes.

VNS is not effective for all patients, and identifying those who will respond favorably has been a challenge. Published in *Epilepsia*, Liu and colleagues examined HRV as a marker of favorable outcome in a cohort of 32 patients undergoing VNS for refractory epilepsy [5]. The study enrolled patients between the ages of 6 and 38 who had undergone VNS implantation, along with 32 age- and gender-matched controls without epilepsy, sleep or autonomic disorders. The researchers used a 12-lead ambulatory electrocardiogram (ECG) monitoring system with a digital sampling rate of 500 samples/second per channel, and recorded for 24 consecutive hours prior to VNS surgery in all subjects. Participants were asked to keep a diary of their activities—ranging from sleeping to exercising—and the activities were codified by type of activity and compared between groups. The authors reported that the amount of time spent on different types of activity during the recording period was not significantly different between subjects or between groups.

HRV results were not significantly different in those who reported seizures during the recording period compared to those who did not. Medication doses were not changed, and the exclusion criteria included “medication(s) that may impact autonomic function,” although this was not explained in further detail. The authors found no difference in HRV in those taking antiepileptic medications with anticholinergic effects. The standard deviation of the RR intervals (SDNN) was significantly lower in the epilepsy group, and those with greater HRV responded more favorably to VNS with greater seizure control. All of the analyzed HRV indices were significantly lower in non-responders (those with no change in seizure frequency) than in their healthy counterparts, with the exception of the mean RR interval and the low frequency/high frequency ratio.

Limitations of this study included a small sample size, a broad age range of subjects (it has been well established that HRV diminishes with age) and the lack of a controlled environment. The authors did their best to control for environmental factors by categorizing activity type and comparing both within and between groups, however it is impossible to truly control for a myriad of environmental confounders. HRV is extremely responsive to

environmental cues and stimuli such as sleep–wake times, eating habits, emotional stress and physical exertion, and all of these factors may have influenced individual results. Nonetheless, Liu and colleagues provide another thought-provoking article in support of HRV as a marker of overall autonomic health, and demonstrate that patients with greater vagal tone may be better candidates for VNS treatment.

Plasma catecholamines in postural tachycardia syndrome: when to measure?

Postural tachycardia syndrome (POTS) is sometimes classified based on the proposed pathophysiology, such as the neuropathic and hyperadrenergic subtypes. In neuropathic POTS, there appear to be signs of a mild small fiber neuropathy and/or mild peripheral sympathetic denervation. In hyperadrenergic POTS, plasma catecholamine levels upon standing or during head-up tilt (HUT) are elevated [6]. Whether these findings are cause, consequence, or epiphenomena is unknown. These differences raise the possibility that certain POTS subtypes may respond differently to therapy. For example, hyperadrenergic POTS patients may potentially respond to beta-blockers rather than intravascular volume replacement.

While the diagnosis of hyperadrenergic POTS requires supine and standing norepinephrine levels, the ideal time to measure the serum catecholamines during HUT is unknown. To address this specific question, Crnošija et al. recently published their analysis of hemodynamic and catecholamine levels in POTS patients during HUT in *Autonomic Neuroscience* [7]. They measured plasma catecholamine levels in supine rest and during HUT at minute 10, 20 and 30. The researchers defined hyperadrenergic POTS as patients who had upright plasma norepinephrine levels >3.5 nmol/L [8]. Patients who met the criteria for hyperadrenergic POTS had plasma norepinephrine levels >3.5 nmol/L at minute 10 of HUT, and the plasma norepinephrine levels did not increase further when measured at minute 20 or 30. Patients who did not have hyperadrenergic POTS did not meet the norepinephrine level threshold at minute 20 or 30 either. Equally importantly, patients with the hyperadrenergic POTS phenotype had a mildly increased or stable systolic blood pressure (SBP) during HUT, unlike the non-hyperadrenergic group, who had a very mild and, non-clinically significant decrease in SBP (in all cases the drop was smaller than 20 mmHg) and reached a supine SBP level at around minute 6. There was no significant difference in heart rate changes between the groups. While acknowledging that these findings are from a small sample of patients (19 patients in the study: seven hyperadrenergic and 12 non-hyperadrenergic), it would be

reasonable to suggest that a single catecholamine level, in contrast to multiple levels obtained at different times, is sufficient to diagnose hyperadrenergic POTS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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