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Loss of Interstitial Cells of Cajal and Patterns of Gastric Dysrhythmia in Chronic Unexplained Nausea and Vomiting

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Background

Chronic unexplained nausea and vomiting (CUNV) encompasses highly symptomatic disorders of unclear etiology. One putative contributing factor is slow wave dysrhythmia, but evaluation has been hindered by a lack of spatiotemporal detail in past recordings. Potential abnormalities in the networks of interstitial cells of Cajal (ICC), which generate and propagate slow waves, have not been explored in CUNV patients.

Aims

To investigate the pathophysiology of CUNV by:

1. High-resolution (HR) *in vivo* slow wave mapping.
2. Immunohistochemical and electron microscopy (EM) analysis of ICC.

Methods

CUNV patients (n=9) with normal gastric emptying, and control patients (n=9), were recruited. Intra-operative serosal HR mapping was performed using validated methods (256 electrodes; 36 cm^2; Figure 1).

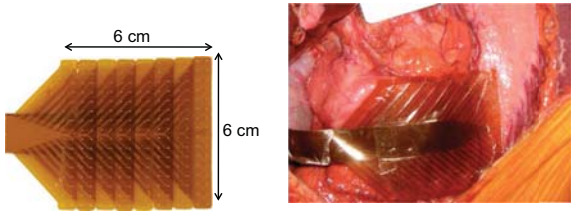

Figure 1: *High-resolution serosal mapping electrodes (left) and intra-operative placement (right).*

Slow wave propagation profiles were defined and dysrhythmic patterns were quantified. Slow wave frequency, velocity, and amplitude were calculated using validated algorithms. ICC cell bodies were identified and quantified by a validated dual-staining approach applied to tissue collected via punch-biopsy after mapping, and ultrastructural features of ICC were analysed by EM. Slow wave and ICC results were compared between CUNV patients and controls.

Results

Slow wave dysrhythmias were identified in all 9/9 CUNV patients, compared with 1/9 controls. Dysrhythmic patterns were spatially complex (Figure 2), and included abnormalities of initiation (ectopic pacemakers; unstable focal activations) and abnormalities of conduction (re-entry; conduction blocks; retrograde propagation; wavefront collisions). Dysrhythmias occurred across bradygastric (<2.4 cycles min^{-1}; 2 pts), tachygastric (>3.7 cycles min^{-1}; 2 pts), and normal frequencies (5 pts),(cohort range: 2.0-5.1 cycles min^{-1}), and exhibited velocity anisotropy (mean 3.3±0.6 mm s^{-1} longitudinal vs 7.6±1.5 mm s^{-1} circumferential, P<0.01). Amplitudes were comparable between CUNV patients and controls (mean 0.30±0.08 mV vs 0.33±0.05 mV, P=0.7).

ICC density was significantly depleted in CUNV patients compared to age-matched controls (P<0.05; Figure 3), and mild ultrastructural abnormalities were observed (Figure 4).

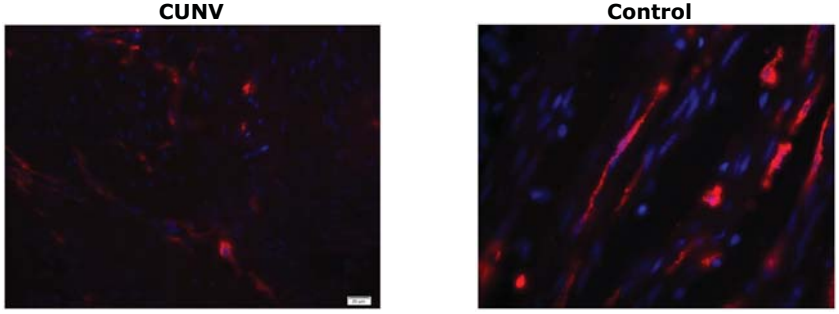

Figure 3: *Comparison of ICC in gastric tissue samples from CUNV patient (left) versus control (right). ICC were stained red and cell nuclei were stained blue, such that ICC bodies could be accurately quantified.*

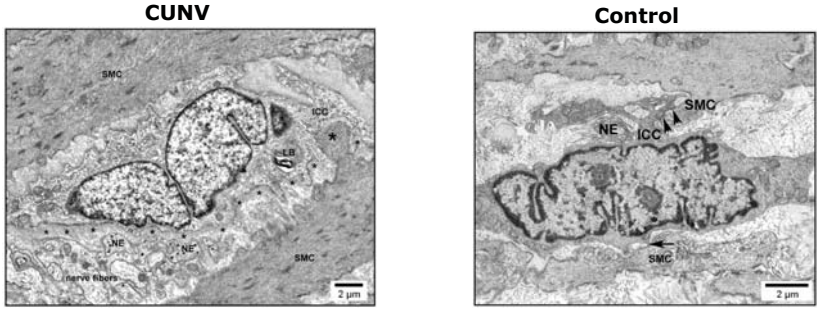

Figure 4: *EM images comparing ICC ultrastructure in a CUNV patient (left) versus control (right). The primary abnormality was a thickened basal lamina (*), particularly near nerve fibers and endings.*

Dysrhythmic Slow Wave Activity

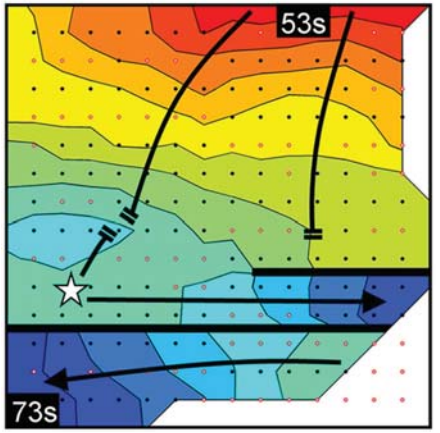

Figure 2: *Example of a dysrhythmic propagation pattern in the gastric corpus. Dots represent electrodes (red = interpolated) and isochrones show area of propagation per 2 s, from red (early) to blue (late). Antegrade propagation at the top of the array is normal, but dysrhythmias are present in the distal mapped area, including: ectopic pacemaker (star), conduction blocks (thick lines), and regions of retrograde and circumferential activation.*

Conclusions

1. **CUNV patients exhibited ICC depletion and ultrastructural abnormalities, in combination with slow wave dysrhythmias.**
2. **Slow wave dysrhythmias were spatially complex and routinely occurred at normal slow wave frequency, thereby likely going undetected by traditional low-resolution recordings.**
3. **These data provide a new pathophysiological characterisation of CUNV, and may inform future diagnostic and therapeutic strategies.**