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Autonomic Priming as a Potential Disease Modifier in Eosinophilic Oesophagitis A Progressive Three-Hit Hypothesis

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Abstract

Eosinophilic oesophagitis (EoE) is an antigen-driven, Th2-mediated inflammatory disorder characterised by oesophageal dysfunction and mucosal eosinophilia (≥15 eosinophils per high-power field). Although epithelial barrier dysfunction and allergen exposure are established pathogenic drivers, significant heterogeneity exists in symptom severity, motility impairment, and therapeutic responsiveness.

This paper proposes that cumulative autonomic injury may function as a disease-modifying substrate capable of lowering inflammatory activation thresholds in antigen-driven oesophageal disease. Sequential autonomic insults—including viral injury, haemodynamic instability, and cardiothoracic surgical stress—may establish sustained parasympathetic impairment and baroreflex dysfunction. Progressive visceral autonomic involvement may impair oesophageal motility, mucosal clearance, and epithelial integrity, thereby facilitating amplification of antigen-driven Th2 inflammatory responses.

A conceptual three-hit model is proposed in which (1) early autonomic disturbance primes visceral regulatory pathways, (2) haemodynamic stress compounds autonomic instability, and (3) subsequent physiological injury consolidates a persistent dysautonomic state capable of modifying immune activation thresholds.

This framework generates testable predictions linking autonomic dysfunction severity to inflammatory burden and disease variability in eosinophilic oesophagitis.

Keywords: Autonomic Dysfunction, Eosinophilic Oesophagitis, Neuro-immune Signalling, Vagus Nerve, Dysautonomia, Baroreflex Instability, Disease Modulation

Key Insights

- Introduces autonomic vulnerability as a potential disease-modifying substrate in EoE.
- Proposes a three-hit autonomic priming model linking sequential physiological insults to regulatory instability.
- Integrates autonomic dysfunction markers such as HRV variability and baroreflex disturbance with oesophageal dysmotility.
- Suggests parasympathetic impairment may lower inflammatory activation thresholds in antigen-driven disease.
- Generates testable predictions linking autonomic dysfunction severity to disease variability and treatment responsiveness.

Introduction

Eosinophilic oesophagitis is increasingly recognised as a chronic inflammatory disorder characterised by immune-mediated epithelial injury and oesophageal dysfunction. Despite growing understanding of the immunological mechanisms underlying EoE, considerable variability remains in symptom severity, motility disturbance, and treatment responsiveness.

These variations suggest the presence of additional physiological factors capable of modifying disease expression.

The autonomic nervous system regulates multiple processes central to gastrointestinal function, including oesophageal motility, mucosal barrier integrity, and inflammatory signalling. Disturbances in autonomic regulation may therefore influence the expression of oesophageal inflammatory disease.

This paper proposes that cumulative autonomic injury may create a physiological environment that lowers inflammatory activation thresholds in antigen-mediated oesophageal disease.

Autonomic Regulation and Gastrointestinal Function

The autonomic nervous system coordinates multiple aspects of gastrointestinal physiology, including:

- oesophageal peristalsis
- gastric emptying
- mucosal secretion
- inflammatory signalling

Parasympathetic vagal pathways play an especially important role in maintaining gastrointestinal regulatory balance.

When parasympathetic activity is diminished and sympathetic tone predominates, motility disturbances and impaired mucosal defence may occur.

Progressive Autonomic Priming

The proposed model suggests that sequential autonomic insults may progressively destabilise regulatory function.

Three stages are proposed.

- **First Hit: Viral Injury**

Certain viral illnesses have been associated with persistent dysautonomia and autonomic instability.

- **Second Hit: Haemodynamic Instability**

Cardiovascular events may impair baroreflex sensitivity and disrupt autonomic regulatory balance.

- **Third Hit: Surgical Physiological Stress**

Major cardiothoracic surgery may introduce additional inflammatory and neural stress, consolidating dysautonomic instability.

Together these events may create a primed physiological state in which inflammatory responses become amplified.

Autonomic Influence on Inflammatory Regulation

Emerging evidence suggests that vagal signalling participates in modulation of inflammatory responses through neuro-immune communication pathways.

Parasympathetic impairment may therefore influence inflammatory signalling thresholds within gastrointestinal tissues.

Conceptual Model

Under the proposed model, cumulative autonomic injury results in:

- reduced parasympathetic tone
- impaired baroreflex regulation
- altered visceral motility
- reduced epithelial clearance mechanisms

These factors may interact to facilitate antigen-driven inflammatory amplification in eosinophilic oesophagitis.

Testable Predictions

The hypothesis generates several predictions:

- Patients with greater autonomic dysfunction should demonstrate greater symptom variability.
- Improvement in autonomic stability may correlate with improvement in gastrointestinal symptoms.
- Multisystem dysautonomic symptoms may be present in subsets of EoE patients.

Limitations

This paper presents a conceptual hypothesis rather than direct experimental evidence. Further physiological and clinical studies are required to evaluate the proposed mechanisms.

Conclusion

Autonomic regulation plays a central role in maintaining gastrointestinal homeostasis. When autonomic integrity is compromised, regulatory instability may influence inflammatory disease expression.

The proposed autonomic priming model suggests that cumulative autonomic injury may function as a disease-modifying substrate in eosinophilic oesophagitis.

Further research exploring interactions between autonomic regulation and inflammatory signalling may provide new insights into the pathophysiology of this condition.

Progressive Autonomic Priming Model

Conceptual model illustrating sequential autonomic insults leading to sustained regulatory instability.

- **Panel A:** Initial autonomic disturbance following viral injury.

- **Panel B:** Baroreflex instability following haemodynamic stress.

- **Panel C:** Consolidation of dysautonomic vulnerability following surgical physiological stress.

The model proposes that cumulative autonomic impairment lowers physiological tolerance thresholds and may modify inflammatory disease expression.

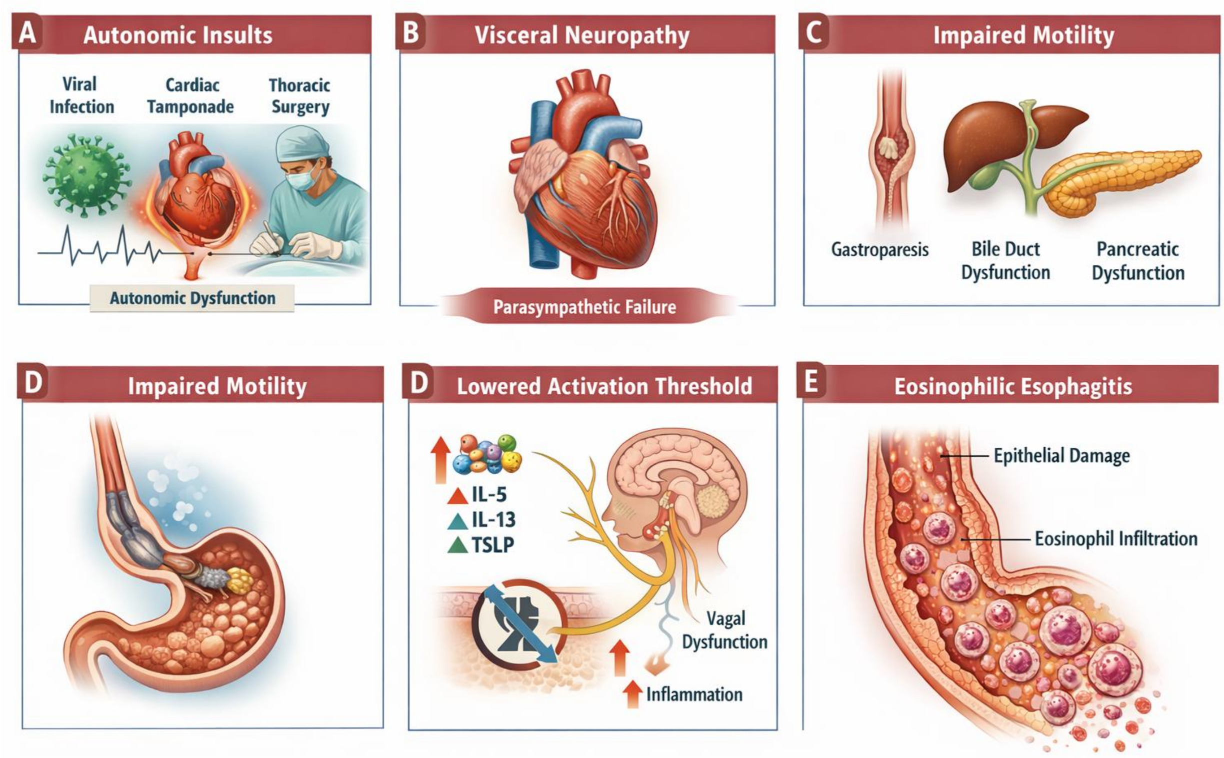

Figure 1

Author Declarations

Author Contribution

Bruce H. Knox: conceptualisation, investigation, literature review, writing, editing, and final approval.

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Conflict of Interest

The author declares no conflict of interest.

Ethics Statement

All information presented in this manuscript is anonymised and used solely for hypothesis generation.

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