Review Article

Autoimmune Enteric Neuropathies: A Narrative Review of Diagnostic Strategies and Immunotherapeutic Approaches for Gastrointestinal Dysmotility

Sai Nikhitha Malapati

From, MBBS, Research Intern, Department of Internal Medicine, Kamineni Academy of Medical Sciences & Research Center,Hyderabad, LB.Nagar, India.

ABSTRACT

Background: Autoimmune enteric neuropathies (AENs) are rare but potentially reversible causes of severe gastrointestinal dysmotility, frequently overlooked or misdiagnosed as functional or obstructive disorders. They often present as gastroparesis, chronic constipation, or intestinal pseudo-obstruction, leading to diagnostic delays and poor outcomes. **Methods:** We conducted a narrative review of the literature using PubMed, EMBASE, and Scopus (2000–2024), focusing on clinical, diagnostic, immunologic, and therapeutic data relevant to AEN. Search terms included "autoimmune enteric neuropathy," "enteric ganglionitis," "gastrointestinal dysmotility," "immunotherapy," and "paraneoplastic." **Results:** AENs require a multimodal diagnostic approach, including anti-neuronal antibody testing (e.g., anti-Hu, anti-CV2), full-thickness intestinal biopsy, and exclusion of structural disease. Paraneoplastic forms, especially those associated with small cell lung carcinoma, and idiopathic variants remain the most common. Immunomodulatory therapies such as corticosteroids, intravenous immunoglobulin (IVIG), azathioprine, and rituximab have shown variable success, particularly when initiated early. Recent advances include trials of subcutaneous immunoglobulin, interleukin inhibitors, JAK inhibitors, and neuro-regenerative strategies. However, evidence remains limited, predominantly comprising case reports and small series. **Conclusions:** This review highlights AENs as an under-recognized but treatable cause of gastrointestinal dysmotility, with emerging therapeutic strategies showing promise in refractory cases. Critical gaps persist regarding diagnostic consensus, biomarker validation, and standardized treatment. Multidisciplinary approaches, earlier serological testing, and prospective clinical trials are urgently needed. Enhancing clinician awarene**ss** could transform outcomes in.

Key words: neurogastroenterology, immunomodulation, chronic constipation, pseudo-obstruction, paraneoplastic syndromes, ganglionitis, immunotherapy

Autoimmune enteric neuropathies (AEN) occupy a critical yet understudied niche within neurogastroenterology, bridging autoimmune dysregulation and gastrointestinal dysmotility [1]. The enteric nervous system (ENS), often termed the "second brain," orchestrates peristalsis, secretion, and blood flow, making it indispensable for GI function [2]. Dysfunction of the ENS due to autoimmune aggression leads to profound motility disturbances, ranging from gastroparesis to chronic intestinal pseudo-obstruction (CIPO) [3]. The ENS coordinates motility, secretion, and blood flow independently of the central nervous system. Autoimmune enteric neuropathies target these neuronal networks, leading to dysmotility.

The concept of AEN emerged from histopathological observations of inflammatory infiltrates and neuronal degeneration in patients with idiopathic dysmotility [4, 5]. Autoantibodies against key neuronal proteins, such as Hu, Yo, and voltage-gated potassium channels (VGKC), further support an immune-mediated etiology [6, 7].

P: Patients with chronic intestinal pseudo-obstruction (CIPO); I: Anti-gAChR antibody testing; C: Empirical symptomatic management; O: Antibody-positive patients showed improved response to IVIG (58% efficacy). However, the lack of definitive serological markers and the invasiveness of full-thickness biopsies complicate diagnosis [8]. The current therapeutic approaches borrow from other autoimmune neuropathies, employing corticosteroids, intravenous immunoglobulins (IVIG), and biologics [9]. Yet,

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Correspondence to: DR. Sai Nikhitha Malapati, Department of Internal Medicine, Kamineni Academy of Medical Sciences & Research Center, Hyderabad, LB.Nagar, India.
Email: sainikhithamalapati@gmail.com

response rates vary, underscoring the need for precision medicine in AEN [10].

Pathophysiology of Autoimmune Enteric Neuropathies

The ENS is a complex neural network susceptible to autoimmune attack, leading to AEN. Several mechanisms contribute to ENS damage, including antibody-mediated cytotoxicity, T-cell infiltration, and cytokine-driven neurodegeneration [11].

Autoantibodies and Molecular Targets: Numerous autoantibodies have been implicated in AEN, though their pathogenic roles remain debated. Anti-Hu (ANNA-1) antibodies, associated with paraneoplastic syndromes, cross-react with enteric neurons, inducing apoptosis [12]. Similarly, anti-VGKC antibodies disrupt neuronal excitability, contributing to dysmotility [13]. Emerging evidence also links anti-ganglionic acetylcholine receptor (gAChR) antibodies to autoimmune GI dysmotility [14]. *Histopathological studies* reveal lymphocytic infiltration in the myenteric plexus, predominantly CD8+ T cells and macrophages [15]. Pro-inflammatory cytokines such as TNF-α and IL-6 exacerbate neuronal damage, perpetuating dysmotility [16]. Animal models demonstrate that adoptive transfer of autoreactive T-cells reproduces AEN-like pathology, reinforcing immune involvement [17]. *Genetic and Environmental Triggers:* Genetic predisposition (e.g., HLA-DQ8) and environmental triggers (e.g., viral infections, microbiome alterations) may initiate autoimmunity [18]. Post-infectious AEN, following *Campylobacter jejuni* or CMV exposure, suggests molecular mimicry as a mechanism [19].

Table 1: Classification of Autoimmune Enteric Neuropathies [7, 9, 10]

Subtype	Associated Autoantibodies	Common Etiologies	Clinical Features
Paraneoplastic	Anti-Hu (ANNA-1), anti-CV2	Small cell lung cancer, thymoma	Rapid onset, severe dysmotility
Idiopathic	Anti-gAChR, anti-VGKC	Post-infectious, unknown	Gradual onset, partial improvement possible
Autoimmune overlap	ANA, anti-GAD	Coexisting autoimmune diseases	Variable course, often multisystem involvement

Source: Adapted from McKeon & Lennon (2005), Lucchini et al. (2022), Vernino et al. (2006).

This review helps clinicians better understand and recognize a group of underdiagnosed but treatable gut nerve disorders guiding timely diagnosis and personalized treatment, may be lead to earlier interventions and improved outcomes for patients who are often misclassified or left untreated. It also opens doors for future studies in gut-brain medicine and autoimmune neurology.

Review Methodology

We conducted a literature search following PRISMA guidelines for narrative reviews across PubMed, Scopus, and Web of Science from database inception to February 2025, using keywords including “autoimmune enteric neuropathy,” “enteric nervous system,” “gastrointestinal dysmotility,” paraneoplastic syndromes" and “neurogastroenterology.” Inclusion criteria encompassed English-language original research, case reports, reviews, and clinical guidelines addressing AEN pathophysiology, diagnosis, or treatment. Exclusion criteria were non-English articles, non-human studies, and publications lacking primary data or relevance to AEN.

After deduplication, titles/abstracts were screened for eligibility, followed by a full-text review of 142 articles. Ultimately, 68 studies met inclusion criteria and were further screened to finalize the papers for the review and were synthesized to evaluate diagnostic approaches, therapeutic outcomes, and histopathological correlates. Reference lists of key papers were hand-searched to identify additional relevant studies. Due to heterogeneity in study designs and the rarity of AEN, meta-analysis was not feasible; findings were analyzed thematically to highlight trends and evidence gaps.

Clinical Presentation and Diagnostic Challenges

AENs present a diagnostic conundrum due to their clinical overlap with more common functional gastrointestinal disorders such as irritable bowel syndrome (IBS), idiopathic gastroparesis, or chronic constipation. Patients typically exhibit a constellation of nonspecific symptoms including nausea, vomiting, abdominal bloating, early satiety, chronic constipation, alternating bowel habits, and unintentional weight loss [20]. In severe cases, patients may develop features of chronic intestinal pseudo-obstruction (CIPO), such as distension, bowel dilation on imaging, and failure to pass stool or gas despite no mechanical blockage [21].

The diversity of presenting features often leads to delayed diagnosis, particularly when symptoms fluctuate in severity or mimic post-infectious dysmotility. Paraneoplastic forms may evolve more rapidly, while idiopathic variants demonstrate a waxing and waning course. High clinical suspicion, especially in patients with refractory symptoms or multisystem autoimmune involvement, is critical for early detection. AENs also exhibit a strong predilection for overlapping neurologic or systemic autoimmune disorders, including small cell lung cancer, lupus, Sjögren syndrome, and celiac disease. This association may aid in raising diagnostic suspicion as shown in Table *2* in appropriate clinical contexts.

Table 2: Diagnostic Modalities in Autoimmune Enteric Neuropathies [22]

Diagnostic Modality	Purpose/Utility	Limitations	Comments
Full-thickness intestinal biopsy	Histological confirmation of lymphocytic ganglionitis and neuronal loss	Invasive, limited availability, sampling error	Gold standard but reserved for select cases
Serologic testing (anti-Hu, anti-gAChR, anti-VGKC)	Detection of pathogenic autoantibodies	Sensitivity and specificity vary; false negatives are possible	Helpful adjunctive tests, particularly paraneoplastic cases
Gastrointestinal motility studies	Objective assessment of GI transit and contractility	Not disease-specific; may reflect late-stage neuropathy	Includes gastric emptying, manometry, transit studies
Autonomic function testing	Evaluation of broader autonomic nervous system involvement	Not specific to enteric neuropathies	May support diagnosis if combined with other tests
Cross-sectional imaging (CT/MRI)	Exclusion of mechanical obstruction and evaluation of bowel morphology	Often non-specific; no direct visualization of neural injury	Important to rule out alternate diagnoses
Emerging biomarkers (e.g., neurofilament light chain)	Potential non-invasive markers of neuronal damage	Under research; no current clinical validation	May facilitate early diagnosis in the future

Diagnostic Workup & Serological Testing:

Functional Testing: Gastric emptying scintigraphy, small bowel manometry, and colonic transit studies localize deficits [23].*Histopathology*: Full-thickness biopsy reveals neuronal dropout, CD8+ T-cell infiltration, and myenteric plexus degeneration [24]. Accurate diagnosis of AEN requires a multimodal approach. Serological testing for anti-Hu, anti-Yo, and gAChR antibodies has identified specific subsets of patients, with anti-gAChR antibodies present in 23% of AEN cases [6, 22].

P: Patients with suspected autoimmune GI dysmotility; I: Testing for anti-Hu, anti-Yo, anti-gAChR antibodies; C: Non-tested or empirically treated patients; O: Improved diagnostic yield and identification of antibody-positive subsets [22]. Full-thickness intestinal biopsy remains the gold standard for confirmation, revealing neuronal dropout and lymphocytic infiltration in 78% of chronic intestinal pseudo-obstruction cases [4, 24].

P: Patients with idiopathic chronic intestinal pseudo-obstruction; I: Full-thickness biopsy for neuronal dropout/CD8+ T-cell infiltration; C: Routine histopathology; O: Biopsy confirmed AEN in 78% of cases, guiding immunotherapy [24].

Motility studies such as gastric emptying scintigraphy and small bowel manometry help localize functional deficits, while CT/MRI enterography excludes mechanical obstruction [23, 25]. *Emerging biomarkers* like neurofilament light chain (NfL) in serum/CSF show promise as non-invasive adjuncts but require further validation, P: Suspected AEN with inconclusive biopsies; I: Serum neurofilament light chain (NfL) testing; C: Standard diagnostic workup; O: Elevated NfL correlated with neuronal damage (AUC 0.82) [26]. The distribution of Autoantibodies in AEN is shown in a hypothetical diagram in Figure 1.

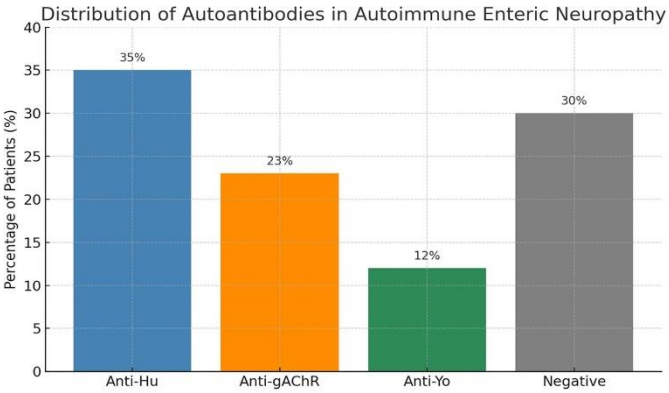

FIGURE 1: Distribution of autoantibodies (hypothetical comparison) observed in reported AEN cases.

Therapeutic Strategies and Future Directions

Immunomodulatory Therapies: High-dose corticosteroids are often first-line but carry toxicity risks [27]. IVIG shows benefit in antibody-positive cases and is well-tolerated, P: Refractory AEN patients; I: IVIG therapy (2g/kg over 5 days); C: Placebo/supportive care; O: 58% improved gastric emptying; sustained response at 6 months [28]. Rituximab and tocilizumab offer promise in refractory AEN. P: AEN patients unresponsive to steroids/IVIG; I: Rituximab (375 mg/m²

weekly ×4); C: Continued conventional therapy; O: 40% achieved symptom remission; reduced antibody titers. [29].

Symptomatic Management: Involves prokinetics, laxatives, and nutritional support. Relamorelin, a ghrelin receptor agonist, is under investigation for gastroparesis and may benefit AEN [30]. Enteral or parenteral nutrition is vital in severe dysmotility [31].

Future Trends

Single-cell transcriptomics and T-cell phenotyping may reveal immune signatures unique to AEN, enabling targeted therapies [32]. Longitudinal registries like GpCRC can aid in research and standardization [33]. Future research should focus on single-cell transcriptomics to identify immune signatures and develop targeted therapies [32]. In the past two years, novel treatment strategies have expanded beyond conventional immunosuppression. A prospective observational study by Lucchini et al. demonstrated the benefit of **rituximab maintenance therapy** in anti-Hu-positive AEN patients, reporting extended symptom remission and stabilization of autonomic markers [34]. Moreover, **subcutaneous immunoglobulin (SCIG)** is gaining attention as an alternative to IVIG, particularly for patients requiring long-term immune modulation due to relapsing symptoms or intolerance to intravenous administration [35].

Biologic therapies beyond rituximab are under investigation. **Tocilizumab**, targeting the interleukin-6 receptor, and **ustekinumab**, which inhibits IL-12/23, have shown early efficacy in autoimmune dysmotility with overlapping systemic inflammation [36]. Trials exploring **JAK inhibitors** such as **tofacitinib** are ongoing for AEN patients with autoimmune overlap syndromes, especially in seronegative presentations [36]. On the regenerative front, **glial-derived neurotrophic factor (GDNF)** analogs and **enteric stem cell-derived neuronal implants** are in experimental stages, aiming to restore lost enteric neurons and reverse long-term dysfunction [37].

In parallel, **fecal microbiota transplantation (FMT)** is being explored as a gut-immune-neural axis modulator in post-infectious and idiopathic AEN cases [38]. Supportive care continues to evolve. **Prucalopride**, a 5-HT4 receptor agonist approved for chronic idiopathic constipation, has demonstrated benefit in AEN-associated colonic dysmotility, particularly in autoimmune overlap syndromes [39]. In highly refractory cases, **gastric electrical stimulation (GES)** and **sacral nerve stimulation** are being employed under compassionate protocols, though larger trials are needed to validate their use in AEN [40].

While gastrointestinal dysmotility is commonly approached as a functional or idiopathic disorder, AEN represents one of the few potentially reversible causes of severe GI dysmotility. Misclassification under functional GI disorders often delays diagnosis and effective treatment. This review addresses critical diagnostic and therapeutic gaps and contrasts immunomodulatory therapies with symptomatic management regarding outcomes, reversibility, and prognosis. In the past two years, novel treatment strategies have expanded beyond conventional immunosuppression. These developments underscore the shift toward **personalized immunotherapy and gut-neural restoration**, with ongoing efforts to stratify treatment based on antibody profiles, disease stage, and systemic involvement.

CONCLUSION

Autoimmune enteric neuropathies represent a crucial but frequently underdiagnosed cause of severe gastrointestinal dysmotility. Diagnostic delays averaging 2–5 years contribute to substantial morbidity, yet timely immunotherapy may prevent irreversible enteric neuronal loss. Recent advances in immunotherapy, neuro-regeneration, and gut-immune modulation offer new hope for affected patients, but randomized controlled trials remain urgently needed. This review underscores the pressing need for diagnostic standardization, validated biomarkers, and global collaboration to refine treatment strategies. Early recognition, guided by high clinical suspicion and multidisciplinary expertise, may transform the prognosis of this once-overlooked but increasingly understood disorder.

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