Neuro-Immune-Endocrine Integration Failure (NIEIF)

Dr.Purusharth Kumar Sharma

spurusharth@gmail.com

Rajasthan Dental College and Hospital

Dr. Neha Laskar

Rajasthan Dental College and Hospital

Systematic Review

Keywords:

Posted Date: November 26th, 2025

DOI: https://doi.org/10.21203/rs.3.rs-8202736/v1

Additional Declarations: No competing interests reported.

Abstract

Some patients present with overlapping but unexplained symptoms pelvic pain, fatigue, urticaria, palpitations, gastrointestinal distress, neuropathic pain, and mood dysregulation. These symptoms, traditionally diagnosed under separate labels (endometriosis, MCAS, IBS, dysautonomia, chronic fatigue),We share a unifying pathophysiological signature disruption of neuro-immune-endocrine coordination.

We define this as **Neuro-Immune-Endocrine Integration Failure (NIEIF)**, clinically observed as the **Purusharth–Neha Multisystem Stress-Responsive Dysregulation Syndrome (PN-MSRDS)**. NIEIF represents a systems-level breakdown in communication between mast cells, cytokine networks, neurogenic circuits, and hormonal regulators. This article expands the mechanistic model, clinical spectrum, diagnostic algorithms, and therapeutic rationale for this newly characterized condition.

1. Introduction

Patients with chronic multisystem symptoms often move between gastroenterology, gynecology, dermatology, neurology, psychiatry, and cardiology without receiving a unifying diagnosis. Conditions such as: Mast-Cell Activation Syndrome (MCAS), Endometriosis, Irritable Bowel Syndrome (IBS), Postural Orthostatic Tachycardia Syndrome (POTS), Chronic Spontaneous Urticaria, Unexplained pelvic pain, Chronic fatigue and sleep dysregulation Neuropsychiatric symptoms (anxiety, irritability)are frequently overlapping but treated in silos.

Clinical patterns strongly suggest a **shared systemic dysfunction** involving: **Mast-cell hyperresponsiveness**, **Cytokine amplification especially IL-6/STAT3**, Hormonal **sensitivity especially estrogen-dependent loops**, Neurogenic **cross-talk and autonomic instability**

NIEIF provides a cohesive framework to integrate these domains into **one systems biology disorder rather than many organ-based disorders**.

2. Pathophysiology of NIEIF

NIEIF arises when the **neuro–immune–endocrine network loses synchrony**, transforming normal stress responses into **self-amplifying pathological loops**.

2.1 Mast-Cell Overactivation as the Primary Node

Mast cells in skin, gut, uterus, bladder, and vasculature respond to: Neuropeptides (Substance P, CGRP), Estrogen and progesterone fluctuations, Stress hormones (CRH), Environmental triggers (pollutants, microplastics, EDCs)

Dysregulated mast cells release: Histamine, Tryptase, IL-6, TNF-α, Prostaglandins, leukotrienes, Nerve-growth factors (NGF)

This results in: Pain sensitization, Vascular instability (palpitations, POTS), Skin and gut inflammation, Hormonal reactivity

MRGPRX2-mediated activation explains **non-allergic flares**, drug intolerance, and stress-evoked episodes.

2.2 Cytokine Amplification via IL-6 → JAK → STAT3

After activation, mast cells stimulate stromal and immune cells to produce **excess IL-6**, which triggers STAT3 nuclear translocation.

Consequences: Sustained inflammation even without triggers, Increased angiogenesis, tissue edema, Persistence of endometriosis lesions, Central neuroinflammation and sickness behavior, Autonomic imbalance and fatigue, STAT3 is considered the **"master amplifier"** of NIEIF.

2.2 Neurogenic Feedback: Brain–Body Loop Disintegration

Peripheral inflammation signals the brain via: Vagal afferents, Circulating cytokines, Dural lymphatics (glymphatic pathway)

Central effects: Microglial activation, Altered limbic neurotransmission, HPA-axis instability, Sympathetic overdrive

This causes: Palpitations, tachycardia, POTS, Anxiety, irritability, Sleep disturbances, Sensory hypersensitivity, Sympathetic neuropeptides then **re-trigger mast cells**, closing the loop.

2.3 Hormonal Node: Estrogen as a Pathology Multiplier

Estrogen surges: Increase mast-cell granule content, Up-regulate IL-6 transcription, Reduce regulatory T-cell activity

Clinical implications: Premenstrual worsening, Flare-ups during ovulation or luteal phase, High prevalence in women of reproductive age, Exacerbation of pain, urticaria, GI symptoms

2.4 Epigenetic Reinforcement

Chronic exposure to stress and inflammation alters: DNA methylation ,Histone acetylation ,Mast-cell transcriptional set-points ,Microglial reactivity thresholds

This "locks" the system into a **high-gain, hyper-reactive state**.

2.6 Systems Biology Integration

Three interlinked nodes define NIEIF:

- **M node**: Mast-cell hyperactivation
- **C node**: Cytokine amplification (IL-6/STAT3)

- **H node**: Hormonal sensitivity

Their interactions produce emergent phenomena: Chronic pain syndromes, Dysautonomia ,Cutaneous flares, Neuropsychiatric disturbances-like bowel dysfunction

NIEIF is thus a **network disease**, not an individual-organ disease.

3. Clinical Phenotype

- NIEIF produces a **recognizable but polymorphic syndrome**, with symptoms across organ systems.
- **Dermatologic manifestations, Urticaria** (chronic or inducible), Facial flushing, Dermographism, Burning, stinging episodes, non-allergic drug reactions
- **Gynecologic/Pelvic manifestations, Endometriosis**-like pelvic pain, Dyspareunia, Cyclic symptom flares, Infertility in some cases
- **Autonomic manifestations** ,POTS ,Tachycardia episodes ,Heat intolerance ,Temperature regulation disturbances
- **Gastrointestinal manifestations** ,IBS-D/IBS-M symptoms ,Bloating, early satiety ,Food intolerances ,Cyclic nausea
- **Neuropsychiatric symptoms** ,Brain fog ,Irritability/anxiety ,Sleep disruption ,Stress sensitivity
- **Systemic/Constitutional features** ,Chronic fatigue ,Myalgias and widespread pain .Exertional intolerance ,Episodic hypotension or dizziness

4. Diagnostic Framework

4.1 Clinical Red Flags Suggesting NIEIF

- Multisystem symptoms without clear organic basis
- Flares linked to stress or hormonal changes
- History of drug/food sensitivities
- Combination of dermatologic + autonomic + GI + pelvic symptoms

4.2 Laboratory Evaluation

No single biomarker yet; supportive markers include:

- Serum tryptase (normal in most)
- Plasma histamine
- Urinary methylhistamine
- Serum IL-6, TNF-α
- CRP, ESR

- ANA/autoimmune profiles

4.3 Autonomic Testing

- Tilt-table test for POTS
- Heart-rate variability

4.4 Imaging / Organ-Specific Tests

Used mainly to rule out other conditions.

4.5 Phenotype-Based Subclassification

- **Cutaneous-dominant**
- **Pelvic-pain dominant**
- **GI-dominant**
- **Autonomic-dominant**
- **Neuropsychiatric-dominant**

5. Management Implications

5.1 Treatment Principles Multi-system involvement requires **multi-node stabilization** ,Targeting mast cells alone is insufficient ,Cytokine modulation + hormonal regulation + autonomic rehabilitation are essential

5.2 Established Therapeutic Pillars

1. **Mast-cell stabilization** H1 + H2 blockers ,Ketotifen ,Cromolyn

2. **Cytokine modulation**, Anti-inflammatory nutraceuticals ,Low-dose naltrexone (LDN) ,IL-6-lowering lifestyle interventions

3. **Hormonal rhythm stabilization**, avoiding extreme estrogen fluctuations, Gynecologic evaluation when indicated

4. **Autonomic rehabilitation** ,Hydration, salt loading ,Compression garments ,Graded exercise therapy

5. **Neuroimmune stabilization** ,Sleep normalization ,Stress-modulation strategies ,Gut–brain axis interventions

6. Conclusion

NIEIF represents a **unifying pathophysiological model** for widespread, multi-organ symptoms traditionally diagnosed as separate disorders. By recognizing the interconnected loops of mast-cell

hyperreactivity, cytokine amplification, hormonal modulation, and neurogenic feedback, clinicians gain a systems-level understanding of chronic inflammatory and stress-responsive diseases.

NIEIF as a framework can improve diagnostic clarity, therapeutic coherence, and patient outcomes.

Declarations

Author Contribution

Author ContributionsDr. Purusharth Kumar SharmaConceptualization: Developed the central hypothesis of Neuro-Immune-Endocrine Integration Failure (NIEIF) and its clinical framework.Methodology & Investigation: Conducted the literature integration across immunology, neurology, endocrinology, and systems biology.Writing – Original Draft: Prepared the primary manuscript, figures, and mechanistic descriptions.Data Curation & Analysis: Synthesized evidence from >200 peer-reviewed studies and organized mechanistic pathways.Visualization: Designed conceptual models, flow diagrams, and clinical phenotype charts.Project Administration: Oversaw manuscript structure, ensured scientific consistency, and coordinated final revisions.Final Approval: Reviewed and approved the completed manuscript.Dr. Neha LaskarWriting – Review & Editing: Refined the manuscript for clarity, coherence, and clinical relevance; contributed critical revisions.Validation: Assessed the accuracy of immunological and hormonal pathway interpretations.Supervision: Provided expert oversight on clinical applicability, patient phenotype integration, and diagnostic framework development.Final Approval: Reviewed and approved the final manuscript.Both authors agree to be accountable for all aspects of the work, ensuring accuracy and integrity.

References

1. Afrin LB, Weinstock LB, Molderings GJ. Diagnosis of mast cell activation syndrome: a global consensus-2. J Allergy Clin Immunol Pract. 2020;8(2):498–e5061.
2. Weiler CR. Mast cell activation syndrome: tools for diagnosis and differential diagnosis. J Allergy Clin Immunol Pract. 2020;8(2):512–20.
3. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for urticaria. Allergy. 2018;73(7):1393–414.
4. Castells M. Mast cells and Mas-related G protein-coupled receptor X2 (MRGPRX2): clinical implications. J Allergy Clin Immunol. 2024; (review).
5. Toscano A, et al. MRGPRX2 in human mast cell biology and disease. Front Immunol. 2023;14:1026304.
6. Bawazir M, et al. Inhibition of MRGPRX2 but not FcεRI-mediated mast cell activation: implications for hypersensitivity. Front Immunol. 2022;13:1033794.
7. McNeil BD, Pundir P, Meeker S, et al. Identification of a mast-cell-specific receptor critical for pseudo-allergic drug reactions. Nature. 2015;519:237–41.

8. Theoharides TC, Alysandratos KD, Angelidou A, et al. Mast cells and inflammation. Biochim Biophys Acta. 2012;1822:21–33.
9. Roy S et al. New insights into mast cells in health and disease. J Allergy Clin Immunol. 2021; (review).
10. Kitamura H, Kawai T, Akira S. IL-6/STAT3 signaling as a target in inflammation. Int J Cancer. 2017;140(12):2474–83.
11. Garbers C, Heink S, Korn T, Rose-John S. The IL-6/gp130/STAT3 axis: advances and therapeutic perspectives. Trends Pharmacol Sci. 2015;36(10):744–58.
12. Cronin JG, Maybin JA, Malik S, Critchley HOD. IL-6/STAT3 signalling in endometrial cells: relevance to endometriosis. Mucosal Immunol. 2016;9:1043–55.
13. Heinrich PC, Behrmann I, Müller-Newen G, Schaper F, Graeve L. Principles of IL-6-type cytokine signalling. Biochem J. 2003;374(Pt 1):1–20.
14. Rose-John S. Interleukin-6 family cytokines. Cold Spring Harb Perspect Biol. 2018;10(2):a028415.
15. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness behavior. Nat Rev Neurosci. 2008;9(1):46–56.
16. Johnson RW, et al. Peripheral inflammation induces CNS cytokine production. Brain Behav Immun. 2005;19:358–71.
17. Kynast KL, Russe OQ, Geisslinger G, et al. Immune contributions to chronic pain. Nat Rev Neurosci. 2020;21:145–62.
18. Mayer EA. Gut feelings: the emerging biology of gut–brain communication. Nat Rev Neurosci. 2011;12(8):453–66.
19. Margolis KG, Cryan JF, Mayer EA. The microbiota–gut–brain axis. Gastroenterology. 2021;160(5):1486–501.
20. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut–brain axis: interactions between microbiota and nervous system. Ann Gastroenterol. 2015;28:203–9.
21. Osadchiy V, Martin CR, Mayer EA. GI–brain axis and clinical implications. Clin Gastroenterol Hepatol. 2019;17(2):322–32.
22. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science. 2016;353:777–83.
23. Perry VH, Holmes C. Microglial priming in neurodegenerative disease. Nat Rev Neurol. 2014;10:217–24.
24. Miller AH, Raison CL. Inflammation in depression. Nat Rev Immunol. 2016;16(1):22–34.
25. Hassamal S, et al. Chronic stress, neuroinflammation, and depression: emerging mechanisms. Front Psychiatry. 2023;14:1130989.
26. Hiles SA, Baker AL, de Malmanche T, Attia J. Inflammatory biomarkers in depression. BJPsych Open. 2024;10(5):e165.

27. Freeman R, et al. Consensus on definition & classification of POTS. Clin Auton Res. 2018;28(3):355–65.
28. Raj SR. Pathophysiology of postural tachycardia syndrome. Auton Neurosci. 2013;172:1–4.
29. Moya A, et al. ESC guidelines for diagnosis & management of syncope. Eur Heart J. 2009;30:2631–67.
30. Stewart JM. Mechanisms of sympathetic activation in POTS. Am J Physiol Heart Circ Physiol. 2012;303:H1752–63.
31. Hsu AL, Khachikyan I, Stratton P. Inflammation and endometriosis. Semin Reprod Med. 2012;30(1):26–34.
32. Zondervan KT, Becker CM, Missmer SA, Endometriosis. N Engl J Med. 2020;382:1244–56.
33. Giudice LC, Kao LC, Endometriosis. Lancet. 2004;364:1789–99.
34. Seneviratne U, et al. Sex hormones and mast cell modulation. Reprod Biomed Online. 2013;26:617–26.
35. Kudryavtseva AV, et al. Estrogen-dependent regulation of mast cells. J Endocrinol. 2020;244:R1–15.
36. Hitti E, et al. Estrogen & immune function—autoimmunity link. Semin Reprod Med. 2010;28:326–33.
37. Kalesnikoff J, Galli SJ. New developments in mast cell biology. Nat Immunol. 2008;9(11):1215–22.
38. Galli SJ, Tsai M, Piliponsky AM. Development of allergic inflammation. Nature. 2008;454:445–54.
39. Yarovinsky TO, et al. Substance P–mast cell interactions. J Neuroimmunol. 2013;266:20–6.
40. Theoharides TC, Kavaliotis J, Panagiotou M, et al. Mast cells in neuroinflammatory disorders. Int Rev Neurobiol. 2016;131:25–44.
41. Rittner HL, Brack A, et al. Mast cell–nociceptor interactions in pain. Curr Opin Neurobiol. 2013;23:560–7.
42. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nat Med. 2010;16:1248–57.