Revista de Neurología

Rev. Neurol. **2026**; 81(11): 57925
https://doi.org/10.31083/RN57925

Letter to the Editor

Beyond Phenotype: An Anatomical-Compartment Framework for Peripheral Neuropathy

Michele Cerasuolo[1,2,*], Gary Antonio Barahona Rodriguez[3]

[1]Division of Human Anatomy, Neuronal Networks Morphology & Systems Biology Lab, Department of Mental and Physical Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", 80138 Naples, Italy
[2]Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, Cambridge, MA 02138, USA
[3]Oncology Clinical Research Program, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA
*Correspondence: michele.cerasuolo@unicampania.it (Michele Cerasuolo)
Academic Editor: Eduardo Gutiérrez Rivas
Submitted: 10 September 2026 Accepted: 29 September 2026 Published: 17 November 2026

Dear Editor,

We read with interest the recent review by Yuba et al. [1], which proposes a pragmatic phenotype-driven framework for the diagnosis and management of peripheral neuropathy. The classification into distal axonopathy, neuronopathy, demyelinating neuropathy, small-fiber neuropathy, autonomic neuropathy, ischemic/infiltrative/inflammatory axonopathy, and focal compressive or entrapment neuropathy provides a clinically useful bridge between presentation and diagnostic testing. We suggest that this approach could be further strengthened by making anatomical-compartment localization an explicit complementary step.

Peripheral nerves are not homogeneous cables but hierarchically organized structures. Disease may preferentially involve the neuronal cell body, axon, Schwann cell-myelin unit, node or paranode, endoneurial microenvironment, perineurium, epineurium, or intraneural microvasculature. The endoneurium, perineurium, and epineurium form distinct structural compartments, while endoneurial microvessels and the perineurium contribute to maintenance of the specialized intrafascicular environment [2]. Peripheral nerve injury can also trigger extracellular-matrix remodeling and neuroglial responses within the spinal cord, involving matrix metalloproteinases and purinergic signaling pathways that may contribute to structural plasticity [3]. Thus, two neuropathies producing superficially similar clinical or electrophysiological abnormalities may originate from anatomically different sites.

This distinction is already evident in several phenotypes discussed by Yuba et al. [1]. Sensory neuronopathies provide a clear example: their non-length-dependent distribution reflects primary involvement of sensory neuronal cell bodies within the dorsal root ganglia rather than a conventional distal dying-back axonopathy [4]. Likewise, autoimmune nodopathies illustrate why the traditional axonal-versus-demyelinating dichotomy may be insufficient. The node of Ranvier, paranodal junction, juxtaparanodal region, and internode constitute specialized domains of the axon-Schwann cell unit, and disruption of nodal or paranodal proteins can produce conduction failure without conventional segmental demyelination [5].

An anatomical-compartment perspective may also clarify ischemic and inflammatory neuropathies. The vasa nervorum and blood-nerve barrier regulate the endoneurial microenvironment; vascular or barrier dysfunction may therefore contribute to focal ischemia, inflammatory-cell trafficking, edema, and secondary axonal injury [2]. At the other end of the spectrum, entrapment neuropathies are intrinsically topographic disorders in which fascicular architecture, surrounding connective tissues, and the anatomical relationships of the nerve within restricted passages influence vulnerability to compression [6].

We therefore propose a simple extension of the phenotype-first approach, moving from the clinical phenotype to the anatomical compartment, then to the underlying pathophysiological mechanism, and finally to the most appropriate targeted diagnostic test. Such a framework would not replace the clinically oriented classification proposed by Yuba et al. [1] but could provide an additional level of mechanistic precision. Electrodiagnostic testing, nerve ultrasound, magnetic resonance neurography, skin biopsy, autonomic testing, and antibody assessment could then be interpreted not only as tools for identifying a neuropathy phenotype, but also as complementary methods for localizing pathology within the structural hierarchy of the peripheral nervous system. In practical terms, phenotype tells us how the neuropathy presents; anatomy helps define where the pathological process resides. Explicitly integrating these two levels may strengthen the connection between clinical neurology, peripheral nerve microanatomy, and increasingly precise structural and molecular diagnostic approaches.

Author Contributions

MC conceived the manuscript, developed the anatomical framework, reviewed the literature, and drafted the manuscript. GABR contributed to the conceptual development and critically revised the manuscript for important in-

Copyright: © 2026 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

tellectual content. Both authors reviewed and approved the final version of the manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Yuba T, Dabbagh A, Sabouri AS. Peripheral Neuropathy: A Phenotype-Driven Review for Diagnosis and Management. Revista De Neurologia. 2026; 81: 48384. https://doi.org/10.31083/RN48384

[2] Ubogu EE. Biology of the human blood-nerve barrier in health and disease. Experimental Neurology. 2020; 328: 113272. https://doi.org/10.1016/j.expneurol.2020.113272

[3] De Luca C, Virtuoso A, Cerasuolo M, Gargano F, Colangelo AM, Lavitrano M, et al. Matrix metalloproteinases, purinergic signaling, and epigenetics: hubs in the spinal neuroglial network following peripheral nerve injury. Histochemistry and Cell Biology. 2022; 157: 557–567. https://doi.org/10.1007/s00418-022-02082-4

[4] Sheikh SI, Amato AA. The dorsal root ganglion under attack: the acquired sensory ganglionopathies. Practical Neurology. 2010; 10: 326–334. https://doi.org/10.1136/jnnp.2010.230532

[5] Eshed-Eisenbach Y, Brophy PJ, Peles E. Nodes of Ranvier in health and disease. Journal of the Peripheral Nervous System. 2023; 28: S3–S11. https://doi.org/10.1111/jns.12568

[6] Schmid AB, Fundaun J, Tampin B. Entrapment neuropathies: a contemporary approach to pathophysiology, clinical assessment, and management. Pain Reports. 2020; 5: e829. https://doi.org/10.1097/PR9.0000000000000829