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Research Article

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From Autonomic Failure to Autonomic Recalibration: Evidence for a Recovery-Sensitive Paradigm in Multifactorial Secondary Autonomic Dysfunction

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Abstract

Background: *Severe multisystem autonomic dysfunction is encountered in primary neurodegenerative disorders but also in acquired, immune-mediated, post-infectious, metabolic and postsurgical conditions. The visual severity of an autonomic phenotype can therefore exceed what can safely be inferred about underlying pathology or prognosis.*
Objective: To examine the literature supporting a recovery-sensitive interpretation of selected forms of severe secondary autonomic dysfunction and to position Multifactorial Secondary Autonomic Dysfunction (MSAD) within that evidence without conflating biological plausibility with diagnostic validation.

Methods: *A targeted narrative review was undertaken using PubMed-indexed literature and publisher databases through 25 September 2026. Searches focused on primary neurodegenerative autonomic failure, autoimmune autonomic ganglionopathy (AAG), POTS and post-infectious dysautonomia, cardiac surgery and autonomic recovery, baroreflex resetting, small-fibre neuropathy, allostatic load and published MSAD frameworks. This was not a systematic review or meta-analysis.*

Results: *The literature supports four distinctions. First, classical autonomic failure in synucleinopathies is legitimately associated with structural neurodegeneration. Second, similarly severe phenotypes can arise through non-degenerative*

Mechanisms: *AAG can produce widespread autonomic failure and show objective improvement with immunotherapy; cardiovascular autonomic indices may recover after major cardiac surgery; and long-term POTS trajectories include improvement, persistence and deterioration. Third, autonomic regulation is dynamic: baroreflex control resets with physiological demand, and some autonomic phenotypes are modifiable by volume expansion, rehabilitation and treatment of causal drivers. Fourth, cumulative-burden and multi-hit concepts are biologically plausible but do not yet validate MSAD as a discrete disease entity.*

Conclusion: *The defensible paradigm shift is not from "degeneration" to "universal reversibility." It is from severity-based inference to mechanism-based prognosis. Severe autonomic dysfunction should trigger differentiation of neurodegenerative disease from acquired regulatory failure, followed by longitudinal assessment of residual recovery capacity. MSAD is best positioned as a testable cumulative-injury framework that requires independent prospective validation.*

prospective multisystem testing, and external validation are now required. The six companion cameos make that architecture auditable and prospectively testable without converting it into a diagnostic, prognostic, or treatment system.

Keywords: Dysautonomia, Autonomic Nervous System, Secondary Autonomic Dysfunction, MSAD, Autonomic Failure, Recovery, Baroreflex, Physiological Reserve, Recalibration, Multi-Hit Model

Central Proposition: Failure is a phenotype, mechanism determines prognosis.

Key Messages

- Autonomic failure describes a clinical phenotype, it does not by itself establish a neurodegenerative mechanism.
- Primary neurodegenerative autonomic disorders remain an essential and well-supported category and should not be minimised by a recovery-sensitive model.
- Profound acquired autonomic failure can be biologically modifiable, as demonstrated most clearly by immune-mediated autonomic disease and by recovery of autonomic indices after major surgery.
- Longitudinal heterogeneity is critical: improvement is possible in selected syndromes, but recovery is neither universal nor synonymous with cure.
- MSAD is currently a published conceptual framework, not an independently validated diagnostic entity.

1. Introduction

The autonomic nervous system maintains moment-to-moment regulation of blood pressure, heart rate, vascular tone, gastrointestinal function, thermoregulation, pupillary responses, urinary function and other homeostatic processes. Dysautonomia is therefore not a single disease but a broad clinical category encompassing disorders of central and peripheral autonomic regulation with primary and secondary causes [1,2]. Severe presentations create a particular interpretive problem. Orthostatic hypotension, bowel and bladder dysfunction, sweating abnormalities, chronotropic limitation and multisystem symptoms may occur in primary neurodegenerative autonomic disorders, yet overlapping phenotypes also occur in immune-mediated, metabolic, post-infectious and other acquired conditions [1,2]. The intensity of dysfunction may therefore be clinically striking while remaining mechanistically ambiguous. The central proposition examined in this paper is that severity should not be treated as a proxy for irreversibility. This proposition underlies the musical narrative "MSAD: The Recalibration," in which the contrast between "destroyed" and "overwhelmed" serves as a metaphor for distinguishing progressive structural loss from severe regulatory dysfunction in a system that may retain biological capacity for recovery. The objective is not to displace established neurodegenerative models. Rather, it is to define the boundary between conditions in which progressive neuronal pathology is the appropriate explanatory framework and conditions in which acquired dysfunction, reversible interference, adaptation, compensation or partial restoration may better explain longitudinal behaviour. The resulting paradigm shift is one of diagnostic differentiation: failure is a phenotype, mechanism determines prognosis.

2. Methods: Targeted Narrative Evidence Synthesis

This paper presents a narrative review and conceptual synthesis rather than a systematic review. Focused searches of PubMed and publisher databases covered literature available through 25 September 2026. Search concepts included "pure autonomic failure," "neurogenic orthostatic hypotension," "autoimmune autonomic ganglionopathy," "POTS long-term outcome," "post-infectious dysautonomia," "cardiac surgery heart rate variability recovery," "baroreflex resetting," "small fibre neuropathy regeneration," "allostatic load," "multi-hit dysautonomia," and "Multifactorial Secondary Autonomic Dysfunction." Priority was given to peer-reviewed reviews, consensus papers, longitudinal studies, systematic reviews and directly relevant recent research. Published MSAD papers were included to define the proposed framework, but were treated as hypothesis-generating sources rather than independent validation. Because this review is conceptual rather than systematic, omission of a study should not be interpreted as evidence of absence.

3. The Traditional View: where the Degenerative Model is Correct

A scientifically defensible paradigm shift begins by stating the established model accurately. Pure autonomic failure (PAF) is a neurodegenerative disorder characterised clinically by autonomic failure and pathologically by predominantly peripheral alpha-synuclein deposition. Some patients later phenoconvert to other synucleinopathies with central nervous system involvement [3]. Multiple system atrophy and Parkinson disease can likewise produce neurogenic orthostatic hypotension and other autonomic manifestations through neurodegenerative mechanisms [2,3]. Accordingly, "progressive autonomic failure" is not an outdated concept, it remains central to autonomic neurology. Neurogenic orthostatic hypotension can reflect impaired central autonomic pathways or loss of peripheral noradrenergic fibres, and its differential diagnosis includes both primary neurodegenerative disorders and secondary autonomic neuropathies [2]. The interpretive error occurs only when the phenotype of severe autonomic failure is allowed to substitute for aetiological diagnosis. A patient can look clinically similar at one time point while harbouring a different biological process. Thus, the traditional degenerative framework should be retained where evidence supports it, but not universalised beyond its evidentiary boundary.

4. Severity is not Mechanism: Evidence from Acquired Autonomic Failure

4.1 Autoimmune Autonomic Ganglionopathy

Autoimmune autonomic ganglionopathy is one of the clearest demonstrations that profound autonomic failure can occur without an inevitably degenerative trajectory. AAG is an acquired immune-mediated disorder affecting autonomic ganglionic transmission and may cause severe orthostatic hypotension, gastrointestinal dysmotility, anhidrosis, pupillary dysfunction and urinary impairment [4,5]. Earlier literature documented responses to plasma exchange, intravenous immunoglobulin and immunosuppression in selected patients, although controlled

trial evidence has historically been limited [4,5]. The 2026 10-year follow-up study by Chiaro and colleagues strengthens this principle. Sixteen seropositive patients assessed longitudinally had widespread autonomic failure at baseline. After immunotherapy, cardiovascular autonomic markers, antibody titres and pupillary light responses improved significantly, and four patients discontinued catheterisation. Relapse and residual impairment nevertheless remained possible [6]. The study does not support universal recovery, but it demonstrates that widespread autonomic failure can be severe, objectively measurable and biologically modifiable. This is the strongest direct support for the conceptual distinction between structural destruction and functional or transmission-related failure. "Overwhelmed" is not a formal pathological term, but as a systems metaphor it captures a key clinical reality: severe dysfunction can arise from mechanisms that interfere with autonomic signalling without requiring progressive neuronal loss.

4.2. Post-Infectious Dysautonomia and POTS

POTS provides a second example of mechanistic heterogeneity. The NIH expert consensus describes POTS as a syndrome with multiple potential contributors, including hypovolaemia, neuropathic mechanisms, excessive sympathetic activation, immune mechanisms and cardiovascular deconditioning [7]. This heterogeneity is conceptually important because it resists a single-lesion explanation. Post-infectious autonomic syndromes have become increasingly visible in the literature, particularly following SARS-CoV-2 infection. Brock and Bosmans proposed a multi-hit hypothesis in Long COVID in which pre-existing susceptibility interacts with an infectious and immune trigger to disrupt autonomic signalling [8]. Their model is explicitly a hypothesis and cannot be generalised to all post-viral dysautonomia. Its importance here is narrower: multi-hit reasoning is already present in contemporary autonomic and post-infectious research. Long-term POTS data published in 2026 further show why prognosis should be framed probabilistically rather than deterministically. Among 44 adults followed for an average of more than 20 years from symptom onset, 2% reported complete resolution, 46% improvement, 25% worsening, 11% no change and 16% a variable course [15]. The most scientifically useful finding is not that POTS "recovers," but that long-term trajectories are heterogeneous. A recovery-sensitive paradigm must therefore preserve the possibility of improvement without turning possibility into promise.

5. Major Surgery and the Reversibility of Autonomic Indices

Cardiac surgery provides an additional model in which a major physiological insult can acutely disrupt autonomic regulation and later show measurable recovery. Brown and colleagues examined heart-rate variability after coronary artery bypass graft surgery and documented recovery between six and twelve postoperative weeks, challenging earlier claims that the postoperative decline in heart-rate variability was irreversible [9]. A 2024 systematic review of heart-rate variability after coronary artery bypass grafting concluded that conventional time- and frequency-domain indices generally decline after surgery and subsequently recover substantially, with many measures approaching preoperative values over the following months [10]. These findings should not be overextended: heart-rate variability is not equivalent to the autonomic nervous system as a whole, and CABG findings do not establish the reversibility of every postsurgical dysautonomia. They nevertheless establish an important physiological principle. Major surgery can produce pronounced autonomic disturbance without requiring a permanent neurodegenerative explanation. Time, rehabilitation, resolution of perioperative physiological stressors and restoration of cardiovascular regulation can change the measured autonomic phenotype.

6. What "Recalibration" can mean Scientifically

"Recalibration" is best used as an integrative physiological description rather than as a single molecular mechanism. The arterial baroreflex itself is dynamic: during exercise it resets in an intensity-dependent manner to regulate arterial pressure around a higher operating point while preserving reflex function [11]. This demonstrates that autonomic control systems can alter operating characteristics in response to physiological demand. In acquired autonomic illness, a recovery phenotype may emerge from several simultaneous processes: restoration of intravascular volume, improved vascular responsiveness, reduced inflammatory or immune interference, improved ganglionic transmission, medication adjustment, cardiovascular reconditioning, altered baroreflex operation, peripheral nerve repair, compensation within surviving pathways and reduced total physiological load. "Recalibration" should be understood as shorthand for this composite process, not as evidence that the nervous system literally returns to a single stored baseline. The same caution applies to the language of neuroplasticity. Plasticity is a legitimate general property of neural systems, but direct evidence that a specific MSAD phenotype recovers through central autonomic neuroplasticity remains insufficient. The strongest current claim is therefore that regulation is dynamic and that some components of secondary autonomic dysfunction are modifiable. The precise contribution of neural plasticity to MSAD remains a research question.

7. Peripheral Small-Fibre Pathology: Degeneration and Regeneration can Coexist

Small sensory and autonomic fibres provide another reason to avoid treating "neuropathy" as synonymous with fixed loss. The joint EFNS/Peripheral Nerve Society guideline on skin biopsy recognises serial assessment of intraepidermal nerve fibres as a means of studying both degeneration and regeneration [12]. This does not imply that all small-fibre autonomic neuropathies regenerate sufficiently to restore function. It establishes that peripheral fibre pathology can be dynamic and that injury and repair are biologically compatible concepts. For a recovery-sensitive autonomic framework, this is an important boundary condition. Structural injury may be present and yet not be absolute, functional recovery can reflect regeneration, compensation, remyelination where relevant, restoration of transmission, or recruitment of residual capacity. Conversely, evidence of irreversible axonal loss would reduce expected recovery. Mechanism again determines prognosis.

8. Physiological Reserve, Cumulative Burden and the Multi-Hit Proposition

The song's repeated imagery of "layer upon layer" and "hit upon hit" corresponds most closely to cumulative-burden models rather than to a single established autonomic disease mechanism. Allostatic load is defined as the cumulative biological burden associated with repeated or chronic adaptation to stressors and has been linked across diverse health outcomes [13]. Although allostatic load is broader than autonomic dysfunction, it provides a recognised systems-level precedent for the idea that multiple burdens can interact over time. Within autonomic medicine, "reserve" is useful conceptually but is not yet a single standardised biomarker. A patient can be relatively stable at rest yet become markedly symptomatic when standing, walking, eating, exercising, becoming dehydrated or encountering heat. Such challenge states expose the difference between baseline function and available compensatory capacity. The concept is therefore clinically intuitive, but formal MSAD research should operationalise reserve rather than assume it. The multi-hit proposition is scientifically credible when stated narrowly: multiple physiological insults may contribute additively or interactively to autonomic dysfunction in selected patients. The stronger claim—that cumulative insults constitute a discrete, reproducible MSAD disease entity—remains unproven. This distinction is essential if the paradigm is to remain falsifiable.

9. Rehabilitation and Modifiable Physiology

The POTS rehabilitation literature provides further evidence that at least some autonomic phenotypes contain modifiable physiological components. Fu and Levine describe cardiovascular deconditioning and hypovolaemia as important contributors in a subgroup of patients and advocate graded physical reconditioning, beginning with horizontal or recumbent exercise where appropriate, together with volume expansion and other non-pharmacological strategies [14]. They also emphasise the need for stronger randomised evidence. These data do not justify reducing POTS to deconditioning, nor do they establish exercise as appropriate for every post-infectious syndrome. Their relevance is conceptual: an autonomic phenotype can change when a modifiable physiological contributor changes. Recovery can therefore arise not only from "healing nerves" but from improved circulatory volume, muscle pump effectiveness, cardiac conditioning, vascular control and central integration.

10. Positioning MSAD within the Literature

Multifactorial Secondary Autonomic Dysfunction was proposed by Knox in 2026 as a framework for patients whose autonomic dysfunction appears to follow cumulative physiological insults rather than a single primary neurodegenerative process [16]. A related three-hit paper described longitudinal recovery flags and interpreted them as evidence that substantial autonomic network capacity had survived [17]. A separate lived-case paper integrated cumulative injury with a central autonomic regulatory model [18]. These publications establish that MSAD is a defined published hypothesis with proposed diagnostic and longitudinal concepts. They do not independently validate the entity. Because the same investigator originated the framework and contributed the principal case-based observations, external replication is now the critical scientific step. This is not a weakness unique to MSAD, it is the normal transition required when an observation-derived framework moves toward a testable clinical construct. The strongest positioning statement is therefore that MSAD is a cumulative-injury framework biologically consonant with recognised secondary autonomic disorders, dynamic autonomic physiology, multi-hit reasoning and cumulative-burden concepts. It remains to be established, however, whether MSAD identifies a reproducible phenotype with predictive validity beyond existing diagnostic categories.

11. Evidence Map: Testing the Claims behind the Recalibration Narrative

Proposition	Evidence status	Interpretation
Severe dysautonomia does not necessarily equal neurodegeneration	Supported	Secondary, immune-mediated, metabolic and other acquired autonomic disorders are established [1,2,4-7].
Profound autonomic failure can improve objectively	Strongly supported in selected disorders	AAG shows objective autonomic improvement with immunotherapy, catheter dependence can lessen in some patients [6].
Autonomic impairment after major surgery can recover	Supported	HRV and related cardiovascular autonomic indices can recover after CABG [9,10].
Autonomic control can reset or adapt	Supported physiologically	Baroreflex operating characteristics reset with exercise and other demands [11].
Peripheral small-fibre pathology is always irreversible	Not supported	Serial skin biopsy can demonstrate degeneration and regeneration [12].
Several insults can interact to produce persistent dysautonomia	Plausible / emerging	Multi-hit models exist in post-infectious disease, cumulative biological burden is established more broadly [8,13].
Autonomic reserve can be "exhausted"	Conceptually useful, not standardised	Reserve is a systems concept, no single validated MSAD reserve metric currently exists.
Recovery equals cure	Not supported	Long-term POTS and AAG data show residual symptoms, relapse and heterogeneous trajectories [6,15].

MSAD is a validated disease entity	Not yet established	Published framework and case-based observations require independent prospective validation [16-18].

12. The Paradigm Shift Stated Precisely

The evidence does not support the claim that severe dysautonomia was historically regarded as uniformly degenerative and has now been shown to be reversible. Contemporary autonomic medicine has long distinguished primary from secondary disorders. The defensible paradigm shift is more precise: prognosis should not be inferred from the severity of autonomic dysfunction alone. The shift can be expressed as three sequential steps. First, retain the degeneration model when evidence supports progressive structural disease. Second, differentiate mechanism through chronology, examination, autonomic testing, biomarkers where available, causal investigation, treatment response and longitudinal observation. Third, where the disorder is acquired and viable autonomic capacity remains, adopt a recovery-sensitive model that allows for adaptation, compensation, treatment response and partial restoration without promising full recovery. This changes the central clinical question. Instead of asking only "How severe is the autonomic failure?", the clinician asks "What mechanism produced the failure, what structures remain functional, and what evidence exists that the trajectory is modifiable?" That is the scientific meaning of recalibration.

13. Clinical Implications

A recovery-sensitive framework has value only if it improves diagnostic discipline. It should encourage active investigation for treatable or modifiable contributors when clinically appropriate, including immune-mediated disease, medication effects, metabolic disorders, volume disturbance, peripheral neuropathy, cardiovascular deconditioning and other secondary causes. It should also encourage repeated objective assessment when the trajectory itself is diagnostically informative. The framework must simultaneously guard against the opposite error. Progressive neurodegenerative disease should not be relabelled as "recalibration" merely because recovery is desired or because symptoms fluctuate. PAF, MSA, Parkinson disease and other disorders require appropriate neurological evaluation when suggested by the phenotype and course. A recovery-sensitive paradigm is therefore not optimistic medicine, it is mechanism-sensitive medicine.

14. Research Agenda for MSAD

To progress from conceptual framework to validated construct, MSAD requires independent prospective testing. At minimum, future studies should define explicit inclusion and exclusion criteria, characterise the timing and nature of putative physiological "hits", document standardised adrenergic, cardiovagal and sudomotor testing, assess small-fibre involvement where indicated, quantify orthostatic and exertional responses, and measure longitudinal functional outcomes. The reserve construct should be operationalised through reproducible challenge paradigms rather than inferred from symptoms alone. Potential approaches include repeated standing or tilt testing, comparisons of walking and recumbent exercise, postprandial challenge, ambulatory blood-pressure and heart-rate monitoring, and repeated use of validated symptom or functional instruments. The aim would be to determine whether reduced capacity under challenge predicts subsequent instability or recovery. Most importantly, MSAD must generate predictions that can fail. Examples include whether defined combinations of prior insults predict a recognisable autonomic phenotype, whether recovery flags correlate with objective autonomic improvement, and whether a cumulative-burden score predicts trajectory beyond established diagnoses. Independent replication would move the framework from plausible narrative to scientific model.

Figure 1. The paradigm shift: Degeneration -> Differentiation -> Recalibration

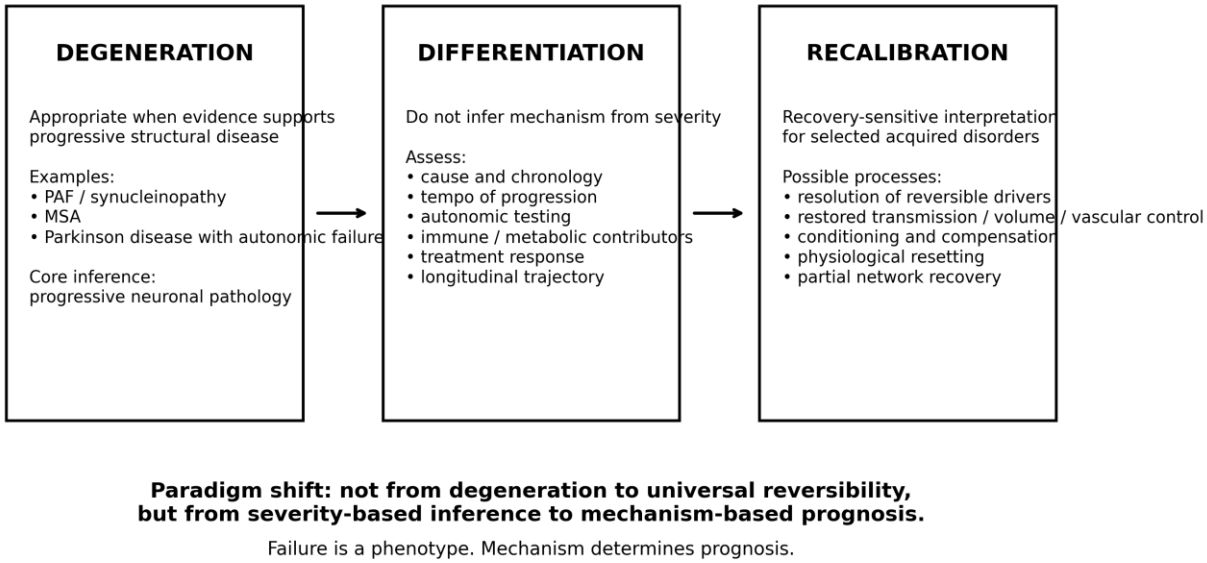


Figure 1: The proposed paradigm shift does not replace neurodegenerative autonomic failure with a universal recovery model. It inserts a required differentiation step between phenotype and prognosis. "Recalibration" applies only where acquired mechanisms and residual biological capacity make modification or recovery plausible.

15. Limitations

As a targeted narrative review, this paper is vulnerable to selection bias. It does not provide the exhaustive search, study-quality grading or pooled estimates expected of a systematic review. Moreover, the evidence is drawn from biologically distinct disorders—AAG, POTS, post-infectious syndromes and postsurgical autonomic changes—which cannot be treated as interchangeable. The term "recalibration" is conceptual and should not be mistaken for an established molecular diagnosis. Likewise, allostatic load and multi-hit models provide systems-level plausibility rather than direct proof of MSAD. Finally, the MSAD literature cited here originates largely from the proposing author, making independent validation essential before the framework can be considered a distinct clinical entity.

16. Conclusion

The literature supports a careful but meaningful shift in how severe autonomic dysfunction is interpreted. Classical neurodegenerative autonomic failure is real and remains the correct framework in disorders such as PAF and related synucleinopathies. Yet severe autonomic phenotypes also arise through acquired mechanisms that may be immune-mediated, post-infectious, metabolic, postsurgical or multifactorial. AAG provides direct evidence that widespread autonomic failure can improve objectively. Cardiac surgery literature demonstrates that marked autonomic disturbance can be followed by recovery of cardiovascular autonomic indices. POTS studies show long-term heterogeneity rather than a single inevitable trajectory. Baroreflex physiology demonstrates dynamic resetting, while rehabilitation and small-fibre research show that components of autonomic impairment can be modifiable. The paradigm shift is therefore not "degeneration versus recovery," but "assumption versus differentiation." Severe dysfunction should prompt investigation of mechanism before prognosis is assigned. Where structural degeneration is demonstrated, the degenerative model should stand. Where dysfunction is acquired and residual network capacity persists, recovery, compensation and recalibration become legitimate scientific possibilities. MSAD is best positioned within this space as a published cumulative-injury framework that is biologically plausible and clinically testable, but not yet independently validated. Its strongest scientific proposition is simple: failure is not mechanism. The next question is not whether the system appears broken, but what remains biologically capable of repair.

Declarations

Consent for Publication: The author consents to publication.

Conflict of Interest: None declared.

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Central Hypothesis: "Reduced repair reserve under autonomic constraint" is proposed as a hypothesis-generating conceptual model and is not presented as an established diagnostic entity.

Ethics and Consent: This perspective is an autobiographical reflection written by the person whose experience is described. It reports no research participants, intervention, or systematically collected research dataset. The author consents to publication of the personal clinical material included here.

Data Availability: No research dataset was generated or analysed for this perspective. Clinical details are presented selectively and narratively, source medical records are not publicly available.

Generative AI and Assistive Communication Disclosure

ChatGPT (OpenAI) was used as an assistive communication and manuscript-preparation tool to support organisation, sentence construction, spelling, transcription, and the conversion of the author's notes, clinical observations, timelines, and narrative accounts into academic prose. This use was intended to mitigate substantial dyslexia-related barriers to writing and sequencing, as well as cognitive fatigue. The author supplied and reviewed the substantive content, clinical facts, interpretations, citations, arguments, and conclusions, retained full editorial control, and accepts responsibility for the manuscript. The tool did not generate research data, determine findings, or qualify for authorship.

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