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Research Article

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Multifactorial Secondary Autonomic Dysfunction (MSAD): A Cumulative-Injury and Autonomic-Reserve Framework for Complex Secondary Dysautonomia

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Abstract

Background: *Autonomic disorders frequently affect cardiovascular, gastrointestinal, thermoregulatory, genitourinary, sleep, cognitive, and exercise domains. In some patients, no single cause adequately explains the onset, severity, fluctuation, and partial recovery of multisystem dysfunction. Multifactorial Secondary Autonomic Dysfunction (MSAD) has been proposed to describe a secondary dysautonomic phenotype in which cumulative physiological insults interact with limited autonomic reserve.*

Objective: *To refine MSAD into a journal-ready, falsifiable clinical framework that distinguishes hypotheses from established evidence and can be tested against recognised primary autonomic and neurodegenerative disorders.*

Approach: *This conceptual review integrates the previously published MSAD framework and first-person longitudinal reports with contemporary literature on orthostatic hypotension, post-viral dysautonomia, cardiac surgery-related autonomic disturbance, autonomic rehabilitation, and the differential diagnosis of neurodegenerative autonomic failure.*

Proposed framework: *MSAD is conceptualised as a threshold disorder of regulation rather than a single pathological lesion. The framework comprises: (1) objective confirmation of autonomic dysfunction; (2) mapping of affected autonomic domains; (3) longitudinal identification of potentially interacting infectious, inflammatory, haemodynamic, metabolic, medication-related, surgical, or deconditioning burdens; and (4) systematic differential diagnosis, including exclusion of primary neurodegenerative autonomic disorders when clinically indicated. Recovery, when it occurs, is predicted to be selective and asynchronous rather than uniform.*

Implications: *The model neither implies that all secondary dysautonomia is reversible nor establishes cumulative injury in any individual patient. Its value lies in organising complex histories, avoiding premature single-cause closure, identifying modifiable contributors, and generating testable longitudinal hypotheses.*

Conclusion: *MSAD is best regarded as an integrative clinical and research framework. Prospective cohorts, validated operational criteria, and biomarker studies are required before it can be considered a distinct diagnostic category.*

Keywords: Dysautonomia, Autonomic Nervous System, Orthostatic Hypotension, Autonomic Reserve, Secondary Autonomic Dysfunction, Post-Viral Dysautonomia, Cardiopulmonary Bypass, Neuroplasticity, Rehabilitation

1. Introduction

Dysautonomia is not a single disease but a clinical descriptor encompassing disturbances of autonomic regulation with diverse mechanisms and trajectories [1-5]. Orthostatic hypotension (OH), postural tachycardia, blood-pressure lability, gastrointestinal dysmotility, thermoregulatory disturbance, and genitourinary dysfunction can arise from neurodegenerative disease, peripheral autonomic neuropathy, systemic illness, medications, volume depletion, deconditioning, immune-mediated processes, and other causes. In patients with hypertension, for example, OH may reflect a combination of impaired autonomic reflexes, altered vascular mechanics, volume status, and medication effects rather than a single mechanism [6]. The emergence of post-viral autonomic syndromes has further highlighted the difficulty of fitting heterogeneous, multisystem presentations into a single-cause model. Contemporary reviews of post-COVID dysautonomia describe a broad, still incompletely understood spectrum in which immune, vascular, autonomic, and deconditioning mechanisms may overlap [7-9]. Cardiac surgery can likewise transiently disturb cardiac autonomic regulation, with heart-rate variability commonly reduced in the early postoperative period and improving over subsequent months in many patients [10]. Although these observations do not establish a cumulative-injury syndrome, they provide a plausible basis for asking whether sequential physiological burdens interact in susceptible individuals. Multifactorial Secondary Autonomic Dysfunction (MSAD) was introduced as an integrative framework for patients whose autonomic failure appears secondary, multidomain, and temporally related to more than one physiological insult [1-5]. This paper does not present MSAD as a validated diagnostic entity. Instead, it refines the concept into a clinically cautious, empirically testable model that separates established autonomic medicine from proposed mechanisms and identifies where prospective evidence remains necessary.

2. Position of MSAD Within Autonomic Medicine

The central distinction is between a descriptive framework and a disease entity, MSAD is proposed as the former. It is intended to organise cases in which multiple secondary contributors plausibly interact, but it should not replace established diagnoses such as neurogenic OH, postural orthostatic tachycardia syndrome (POTS), autoimmune autonomic ganglionopathy, diabetic autonomic neuropathy, pure autonomic failure (PAF), Parkinson disease with autonomic failure, or multiple system atrophy (MSA). This distinction matters because severe, multidomain autonomic failure can occur in progressive synucleinopathies. MSA is an adult-onset, progressive neurodegenerative disorder in which cardiovascular or urological autonomic failure may accompany parkinsonism and/or cerebellar syndrome [10-13]. PAF is also a neurodegenerative synucleinopathy, usually presenting with OH and potentially broader autonomic failure [14]. Although partial improvement may weigh against rapidly progressive neurodegeneration in some circumstances, improvement alone cannot exclude a primary autonomic disorder. Formal neurological assessment and appropriate testing remain essential when the clinical picture raises that possibility.

3. The Proposed Cumulative-Injury and Autonomic-Reserve Model

3.1. Autonomic Reserve

The working construct of autonomic reserve refers to the capacity of distributed autonomic networks and effector organs to maintain homeostasis under physiological stress. It is a conceptual variable rather than a currently validated clinical measure. Reserve may be influenced by age, cardiovascular status, inflammatory burden, metabolic disease, medication exposure, sleep, conditioning, prior illness, and baseline neurological vulnerability. The model predicts that two patients exposed to the same insult may experience markedly different autonomic consequences because their pre-insult reserve and concurrent burdens differ.

3.2. The Multi-Hit Proposition

The multi-hit proposition holds that sequential or overlapping insults may produce greater autonomic dysfunction than any single insult would predict in isolation. Candidate burdens include severe infection, systemic inflammation, haemodynamic compromise, major surgery or critical illness, prolonged immobility, medication effects, metabolic disease, and recurrent physiological stress. “Hit” is therefore a heuristic term, not a claim that every exposure directly injures autonomic neurons. Some hits may act through inflammation, others through vascular or baroreflex disturbance or deconditioning, and still others by reducing compensatory capacity.

3.3. Threshold Decompensation and Partial Recovery

In the proposed model, symptoms become clinically evident when compensatory capacity is exceeded. The resulting phenotype may include cardiovascular instability alongside gastrointestinal, thermoregulatory, genitourinary, fatigue, sleep, or cognitive manifestations. If relevant drivers resolve or can be treated, some functions may improve. Persistent deficits may reflect incomplete recalibration, fixed injury, ongoing disease, medication effects, organ-specific pathology, or a combination of these. The model therefore predicts neither inevitable recovery nor inevitable progression.

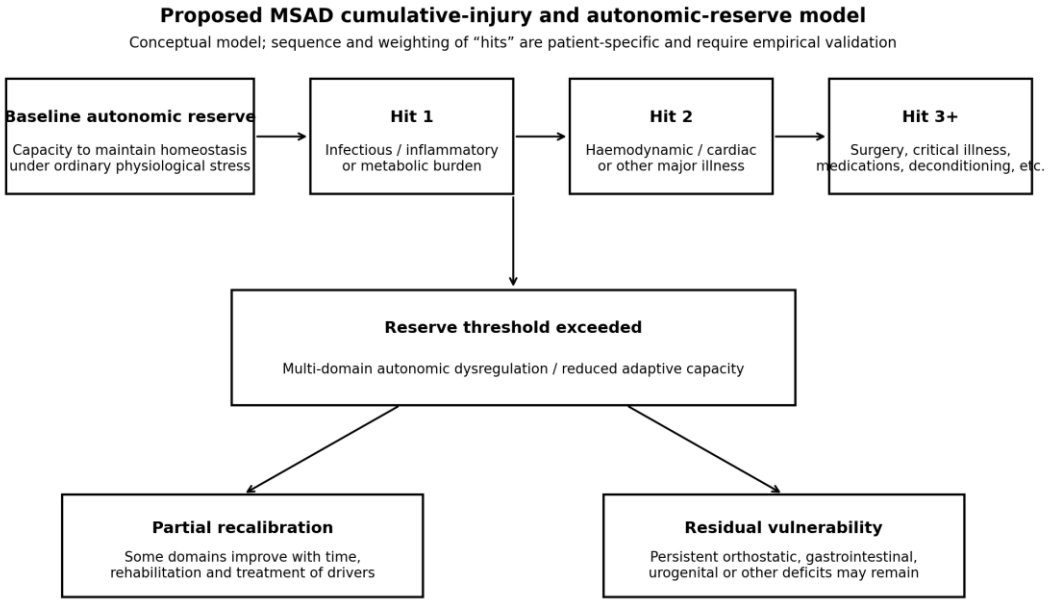


Figure 1: Proposed MSAD Cumulative-Injury and Autonomic-Reserve Model

The figure is conceptual. The number, timing and biological weight of contributing insults are expected to vary between individuals, and the threshold construct requires prospective validation.

4. Proposed Sequential Diagnostic Assessment Framework

The original MSAD work proposed a sequential approach intended to avoid treating the diagnosis as a residual label applied only after all other possibilities have failed [1,2]. For journal use, the framework is best expressed as four clinical questions rather than as validated criteria.

Step	Core question	Examples of evidence / output
Step 1: Confirm dysfunction	Is there objective or reproducible evidence of autonomic dysfunction?	Orthostatic vital signs, active stand or tilt testing, beat-to-beat haemodynamics, autonomic reflex testing, sudomotor testing, domain-specific investigations as clinically indicated.
Step 2: Map domains	Which autonomic and related functional domains are affected, and how severe is impairment?	Cardiovascular, sudomotor/thermoregulatory, gastrointestinal, genitourinary, chronotropic/exercise, pupillary, sleep and symptom-linked cognitive domains.
Step 3: Build a longitudinal burden map	What illnesses, procedures, haemodynamic events, medications or systemic disorders preceded or perpetuated the syndrome?	Construct a dated chronology, distinguish documented events from retrospective inference, identify ongoing reversible contributors.
Step 4: Test alternatives	Does an established diagnosis better explain the phenotype or require specific exclusion?	Review medication and volume status, assess neuropathy, endocrine/metabolic and cardiac causes, evaluate autoimmune and neurodegenerative disorders when indicated, avoid diagnosing MSAD by default.

Table 1: Proposed four-step MSAD Assessment Framework

A previously proposed "three-domain rule" and "insult index" may be useful as research variables, but they should not yet be presented as validated diagnostic thresholds. A publishable operational study would need to define these measures prospectively, test inter-rater reliability, and determine their sensitivity and specificity against comparison groups.

5. Multi-Domain Phenotyping

MSAD assumes that a cumulative secondary process may be easier to recognise when patients are phenotyped across domains rather than through a single symptom. This approach is consistent with the multisystem nature of autonomic physiology, but the domains below should be treated as a framework for structured history-taking and testing rather than as proof of a common cause.

Domain	Illustrative manifestations	Potential assessment
Cardiovascular / vasomotor	Orthostatic hypotension, postural intolerance, BP lability, presyncope/ syncope	Supine and standing BP/HR, active stand or tilt, beat-to-beat BP, Valsalva and other autonomic reflex tests where available
Sudomotor / thermoregulatory	Heat intolerance, altered sweating, paradoxical sweating patterns	Clinical history, thermoregulatory sweat test, QSART or other sudomotor testing where available
Gastrointestinal	Early satiety, nausea, constipation, diarrhoea, suspected dysmotility	Directed gastroenterological evaluation, gastric emptying or motility studies when clinically justified
Genitourinary	Hesitancy, retention, incomplete emptying, urgency or incontinence	Post-void residual, urological assessment and urodynamics when indicated
Chronotropic / exercise	Inappropriate HR response, severe exercise intolerance, orthostatic exercise limitation	ECG/Holter, exercise testing, CPET in selected patients, functional observation
Sleep / fatigue / cognitive symptoms	Non-restorative sleep, fatigue, "brain fog", symptom worsening with orthostatic or exertional stress	Clinical correlation, screen for alternative sleep, neurological, psychiatric and medication-related explanations

Table 2: Clinical Domains Relevant to an MSAD Phenotype

6. Selective and Asynchronous Recovery: A Testable Hypothesis

The source manuscript proposed a fixed hierarchy in which thermoregulation and chronotropic competence recover earlier than baroreflex, gastrointestinal, and bladder control. The longitudinal observations motivating that idea are clinically interesting, but current evidence does not justify universal time windows such as "6-12 months" or "24+ months" [3-5,15]. A stronger journal formulation is that recovery may be selective, asynchronous, and domain-specific. Several factors make this biologically plausible. Autonomic functions are mediated through different combinations of central nuclei, peripheral fibres, vascular effectors, enteric networks, endocrine systems, and behavioural compensations. Cardiac autonomic measures can recover over months after surgery in many patients, whereas persistent OH may reflect ongoing vasoconstrictor failure, altered volume regulation, or medication interactions [6,10]. Post-viral dysautonomia is similarly heterogeneous: objective testing may show substantial dysfunction in some cohorts and relatively little in others [7-9]. The MSAD recovery hypothesis therefore predicts that, within an individual, longitudinal improvement will not necessarily proceed at the same rate across all autonomic domains. A key empirical test would involve repeated, domain-specific autonomic measurements in a prospective cohort rather than reliance on symptom recall alone.

Domain	Proposed pattern	Current evidential status
Thermoregulatory / sudomotor	May improve after the acute inflammatory or critical-illness phase in some patients	Hypothesis supported mainly by case-level observation, requires serial objective testing.
Chronotropic / exercise	May improve with recovery, reconditioning and improved cardiovascular regulation	Supported indirectly by postoperative HRV literature and POTS rehabilitation studies, not specific to MSAD [10-12].
Baroreflex / orthostatic BP control	May remain impaired or fluctuate despite improvement elsewhere	Consistent with recognised complexity of OH, persistence does not by itself establish structural baroreceptor injury [6].
Gastrointestinal / genitourinary	May recover slowly, remain partially impaired, or reflect independent organ-specific pathology	Requires objective domain-specific investigation, cannot be assumed to share one mechanism.

Table 3: Proposed Recovery Patterns and Evidence Status

7. A Longitudinal Case as a Hypothesis-Generating Exemplar

Previously published first-person work described a longitudinal syndrome interpreted through a three-hit sequence: a probable chikungunya-related inflammatory illness, later cardiac tamponade with major haemodynamic compromise, and emergency open-heart repair involving cardiopulmonary bypass [3-5]. The subsequent course included severe multi-domain autonomic dysfunction followed by partial improvement over several years. This trajectory motivated the concepts of cumulative burden, autonomic reserve and selective recovery. The case should be interpreted cautiously. A single longitudinal narrative cannot establish that each event caused a specific component of the subsequent dysautonomia, quantify the relative contributions of infection, shock, surgery, medications, or deconditioning, or exclude coincident disease solely on the basis of the recovery pattern. Its scientific value lies in generating a structured causal hypothesis and identifying measurements that future cases and cohorts should collect prospectively. For journal publication, clinical claims should be restricted to documented medical records and previously published observations. Assertions in the source draft regarding

laboratory confirmation of chikungunya, negative alpha-synuclein biomarkers, TSPO-PET evidence, serial IL-6/TNF-alpha values, or a specific 75% final capacity should be included only if the underlying records exist and can be ethically reported. They are therefore not treated as established facts in this manuscript.

8. Clinical Management Implications

Because MSAD is a framework rather than a treatment diagnosis, management should follow the best-supported treatment for the patient's actual phenotype and identified causes. The following principles are defensible across several forms of orthostatic and secondary autonomic dysfunction:

- Identify and treat reversible aggravating factors, including dehydration, anaemia, medication effects, endocrine or metabolic disease, infection and cardiac contributors where relevant.
- Characterise orthostatic blood-pressure and heart-rate patterns before escalating therapy. In patients with coexisting hypertension or supine hypertension, treatment of OH requires particular care because interventions that raise upright pressure can worsen resting hypertension [6].
- Use non-pharmacological measures such as individualized fluid/salt strategies, compression and physical countermeasures when appropriate to the patient and clinical context [6,11].
- When exercise rehabilitation is used for orthostatic intolerance, begin with an individualized programme, horizontal or recumbent exercise can reduce orthostatic stress in selected patients, with gradual progression as tolerated [11,12].
- Avoid converting mechanistic hypotheses into routine treatment claims. The source draft proposed "microglial stabilizers", immunomodulators and other neuroimmune interventions as general MSAD therapy. Current evidence is not sufficient to recommend these as a standard MSAD treatment strategy, any such treatment should be tied to a recognised indication and appropriate specialist care.

9. Application to Post-Viral Syndromes and Long COVID

Post-viral syndromes provide an important context in which to test the MSAD framework, not a population to which the framework should be presumed to apply. Reviews of post-COVID dysautonomia emphasise heterogeneity, incomplete mechanistic understanding, and variable objective findings [7-9]. Treatment evidence remains limited, a 2025 scoping review found that many intervention studies were small and uncontrolled, whereas guidelines and position statements most consistently addressed exercise or rehabilitation, fluid and salt intake, and compression [9]. MSAD may frame a useful research question: among patients with post-viral autonomic symptoms, do those with additional major physiological burdens—such as surgery, severe haemodynamic events, metabolic disease, or prolonged immobilisation—show a distinct phenotype, greater domain burden, altered recovery trajectory, or different response to rehabilitation? This question is testable in prospective datasets and is more defensible than asserting that post-viral dysautonomia is inherently multifactorial in every patient.

10. Testable Predictions and Research Agenda

A conceptual framework becomes scientifically useful only when it generates predictions that can be disproved. The MSAD model yields the following research propositions:

- Burden-response hypothesis: greater independently verified cumulative physiological burden will be associated with greater multi-domain autonomic impairment after accounting for age, medications and comorbidity.
- Reserve hypothesis: pre-existing markers of reduced cardiovascular or autonomic adaptability will modify the relationship between later insults and dysautonomia severity.
- Asynchronous-recovery hypothesis: repeated objective measures will show discordant recovery slopes across autonomic domains within the same patient more often than would be expected from measurement variability alone.
- Trajectory hypothesis: a subgroup with secondary cumulative injury will show stabilization or partial recovery without the evolving motor/cerebellar phenotype expected in MSA, while a different subgroup may later fulfil criteria for established neurodegenerative disease.
- Clinical-utility hypothesis: structured longitudinal burden mapping will improve diagnostic confidence, identification of reversible contributors, and patient-reported coherence of care compared with unstructured single-specialty assessment.

Priority study designs include prospective longitudinal cohorts, case-control comparisons with PAF/MSA and common non-neurogenic OH, Delphi development of operational MSAD criteria, inter-rater reliability testing, and validation of a multidomain assessment instrument. Studies should prespecify which variables represent symptoms, objective autonomic measures, and mechanistic biomarkers.

11. Limitations

The MSAD framework currently rests on conceptual synthesis, published first-person longitudinal observations, and extrapolation from adjacent autonomic literature. There is no validated MSAD biomarker, established diagnostic code, agreed minimum number or timing of physiological "hits", or evidence that a single mechanism explains all multidomain manifestations. Recovery may reflect natural history, rehabilitation, resolution of acute illness, medication changes, treatment of comorbidities, or regression to the mean. Conversely, some patients with apparently secondary autonomic dysfunction may later prove to have a neurodegenerative, autoimmune, or genetic disorder. These limitations require conservative language and longitudinal reassessment.

12. Conclusion

Multifactorial Secondary Autonomic Dysfunction is most defensible as a proposed integrative framework for complex secondary dysautonomia rather than an established disease entity. Its central claim is modest: in selected patients, multiple physiological burdens may interact with limited autonomic reserve to produce multidomain regulatory dysfunction, and recovery—when it occurs—may be selective and asynchronous.

The framework encourages clinicians and researchers to combine objective autonomic testing with longitudinal burden mapping and rigorous differential diagnosis. Its future value will depend on prospective validation, reproducible operational criteria, and direct comparison with established causes of autonomic failure.

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 difficulties with 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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