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Autonomic Neuropathy within the NOx (Knox) Framework Hypothesis: A Case-Based Reappraisal of Deterministic Neurodegenerative Assumptions

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Abstract

Autonomic neuropathy has traditionally been interpreted within clinical neurology as a progressive and frequently irreversible condition, often assumed to phenoconvert into neurodegenerative disease [1-5]. This paper integrates a longitudinal patient case (2020–2026) with a structured review of medical literature to demonstrate that such deterministic interpretations are not consistently supported by evidence [8–10]. Through the NOx (Knox) Framework Hypothesis, autonomic dysfunction dysautonomia is reconceptualised as a system-level regulatory disturbance with multiple potential trajectories, including stabilisation, fluctuation, and partial or complete recovery [3,10].

Keywords: Autonomic Neuropathy, Dysautonomia, Orthostatic Hypotension, Nox Framework, Knox Hypothesis, Phenoconversion, Neurodegeneration, Systems Medicine, Post-Viral Dysautonomia, Autonomic Instability

1. Introduction

The interpretation of chronic autonomic dysfunction as a predominantly neurodegenerative process has shaped clinical reasoning and patient expectations for several decades [3–5]. Within this paradigm, autonomic neuropathy is frequently understood as an early manifestation of progressive neurological disease, particularly in association with synucleinopathies such as Parkinson's disease and multiple system atrophy [4,5]. However, this interpretation reflects a convergence of historical emphasis and observational bias rather than a universally applicable biological reality [1,2]. The NOx (Knox) Framework Hypothesis challenges this deterministic model by proposing that chronic physiological conditions arise from interacting system instabilities rather than linear disease pathways. Within this framework, autonomic dysfunction is understood as a manifestation of regulatory imbalance within complex physiological systems rather than a terminal diagnosis [3,10]. This distinction separates phenotype from pathway and allows for multiple potential outcomes, including recovery and stabilisation alongside progression [3].

2. Case Integration: A Longitudinal Challenge (2020–2026)

Between 2020 and 2022, progressive orthostatic hypotension led to repeated clinical diagnoses of autonomic neuropathy, a condition commonly associated with neurodegenerative processes in clinical literature [6,7]. These diagnoses were accompanied by the expectation of phenoconversion into irreversible neurodegenerative disease, reflecting prevailing clinical interpretations [4,5,11].

However, longitudinal follow-up through 2026 demonstrates no evidence of neurodegenerative phenoconversion. Instead, the condition has persisted in a non-linear and variable form, characterised by functional adaptation rather than progressive decline. This divergence challenges the assumption that autonomic neuropathy inherently follows a degenerative pathway and aligns with literature indicating variability in progression and outcome [1,8].

3. Autonomic Neuropathy as a Multi-Pathway Condition

Autonomic neuropathy is well established as a heterogeneous condition with multiple etiologies and outcomes [1,8]. Neurodegenerative conditions such as Parkinson's disease and

multiple system atrophy represent one pathway, characterised by progressive decline [4,5].

However, alternative pathways are widely documented. Metabolic causes, particularly diabetes, demonstrate variable progression and may stabilise with appropriate control [8]. Immune-mediated conditions, such as autoimmune autonomic ganglionopathy, frequently show partial reversibility with treatment [9]. Functional and regulatory disorders, including baroreflex dysfunction, are non-degenerative and dynamic [6,7]. These findings indicate that autonomic neuropathy represents a spectrum of conditions rather than a single disease entity, and therefore cannot be reduced to a deterministic trajectory.

4. Emergence of a Deterministic Narrative

Historical and contemporary literature reveals that the association between autonomic neuropathy and neurodegeneration developed through cumulative emphasis rather than explicit universal claims [2,3]. Foundational descriptions of pure autonomic failure correctly identified it as a neurodegenerative disorder [12]. However, subsequent literature and educational materials increasingly prioritised these models, often without equivalent representation of alternative pathways [3]. The emergence of research on phenoconversion further reinforced this perspective by focusing on progression to Parkinson's disease or related disorders [11]. While such studies did not claim inevitability, their framing contributed to a perception of expected progression. Educational condensation of complex information into simplified teaching models further reinforced this narrative, often underrepresenting variability and uncertainty.

5. Terminological Compression and Conceptual Ambiguity

A key factor sustaining deterministic interpretations is the conflation of autonomic neuropathy with pure autonomic failure and related neurodegenerative conditions [2,12]. Autonomic neuropathy is a broad descriptor encompassing multiple etiologies, whereas pure autonomic failure is a specific neurodegenerative disorder associated with alpha-synuclein pathology [4,5]. The inconsistent use of these terms has blurred distinctions between heterogeneous and mechanistically distinct conditions. This terminological compression has reinforced the perception of a unified disease pathway, obscuring variability and contributing to overgeneralisation in clinical interpretation.

6. A Systems-Based Model of Multifactorial Dysautonomia

A systems-based perspective recognises autonomic dysfunction as an emergent property of interacting physiological stressors [3,10]. These may include metabolic disturbance, immune activation, cardiovascular instability , and post-infectious dysregulation [6-7,9,10]. Within this model, autonomic instability arises from cumulative system stress rather than a single pathological cause. Outcomes are therefore determined by the balance between stressors and adaptive capacity, resulting in variable and non-linear trajectories [3]. This framework aligns with the NOx hypothesis and provides an explanation for cases demonstrating stabilisation or improvement over time.

7. NOx Framework Reinterpretation

The traditional model conceptualises autonomic neuropathy as a linear progression toward neurodegeneration. In contrast, the NOx Framework proposes that autonomic instability may follow multiple trajectories, including recovery, stabilisation, fluctuation, or degeneration. Neurodegeneration is therefore understood as one possible outcome within a broader spectrum rather than the default pathway.

8. Case Reinterpretation

The case trajectory from 2020 to 2026 is consistent with a non-degenerative autonomic instability pathway. The persistence of dysfunction without structural neurological decline supports a system-level interpretation rather than progressive neurodegeneration. This provides real-world evidence that phenoconversion is not inevitable and supports a multi-pathway conceptual model.

9. Discussion

The prevailing interpretation of autonomic neuropathy as a predominantly neurodegenerative condition has exerted a substantial influence on both clinical reasoning and patient expectation. However, the findings presented in this manuscript, integrating longitudinal case observation with historical and contemporary literature, demonstrate that this interpretation is not universally supported by empirical evidence [1,8–10]. Rather, it reflects a historically reinforced but conceptually incomplete model shaped by selective emphasis within the literature, diagnostic pattern recognition, and terminological ambiguity [2,3].

9.1. Re-evaluating the Deterministic Paradigm

A central argument of this work is that the association between autonomic neuropathy and neurodegeneration, while valid in specific contexts, has been generalised beyond its evidentiary limits. Neurodegenerative conditions, including synucleinopathies, clearly represent one important pathway of autonomic dysfunction [4,5]. However, the extrapolation of this pathway to autonomic dysfunction as a whole has contributed to a deterministic interpretive framework in which progression is implicitly expected. This manuscript challenges that assumption by demonstrating that the clinical phenotype of autonomic instability does not uniquely specify underlying pathology. Similar presentations may arise from fundamentally different mechanisms, including metabolic, immune-mediated, post-infectious, and functional regulatory disturbances [8–10]. Consequently, phenotype alone cannot be relied upon to infer trajectory, and the presumption of inevitable neurodegeneration represents an overextension of condition-specific evidence.

9.2. The Role of Historical Framing and Terminological Compression

The persistence of deterministic interpretations can be understood in part through the historical evolution of the field. Early descriptive medicine prioritised observable clinical syndromes over mechanistic differentiation , while later advances in neurodegenerative research introduced highly visible and clinically

significant models of progression [4,5,13]. The convergence of these traditions, combined with the broad and often imprecise use of the term "autonomic neuropathy," resulted in a form of terminological compression in which heterogeneous conditions were conceptually grouped under a single implied trajectory [2,12]. This process did not arise from explicit claims of inevitability, but rather from cumulative emphasis and educational simplification. As a result, a probabilistic association was gradually reframed, both implicitly and in practice, as an expected outcome. The analysis presented in Appendix 1 demonstrates that this shift reflects the evolution of medical understanding rather than a definitive biological principle.

9.3. Evidence for Multi-Pathway and Non-Linear Trajectories

A key contribution of this manuscript is the integration of contemporary dysautonomia literature with longitudinal case evidence to support a multi-pathway model of autonomic dysfunction. Current research increasingly recognises that dysautonomia encompasses a spectrum of conditions arising from diverse mechanisms, including post-viral syndromes, autoimmune processes, metabolic dysregulation, and cardiovascular instability [8–10]. Importantly, these conditions exhibit heterogeneous clinical trajectories. While some cases demonstrate progressive decline consistent with neurodegenerative disease, others show stabilisation, fluctuation, or partial recovery over time [10]. The longitudinal case presented here, extending over a six-year period without evidence of neurodegenerative phenoconversion, provides real-world support for this variability and directly challenges deterministic expectations. This divergence between expected and observed trajectories highlights a critical limitation of single-pathway models and reinforces the need for a framework capable of accommodating complexity and variability.

9.4. The NOx (Knox) Framework as a Systems-Based Alternative

Within this context, the NOx (Knox) Framework is proposed as a conceptual model that reframes autonomic neuropathy as a manifestation of system-level regulatory instability rather than as a discrete disease entity. This approach aligns with emerging systems-based perspectives in physiology, which emphasise the interaction between neural, cardiovascular, immune, and metabolic processes in maintaining autonomic balance [3,10]. The framework introduces two key propositions. First, autonomic dysfunction arises from the interaction of multiple physiological stressors rather than from a single pathological driver. Second, clinical outcomes are determined by the dynamic balance between these stressors and the system's adaptive capacity, resulting in divergent trajectories that may include progression, stabilisation, fluctuation, or recovery. Importantly, this model does not reject the role of neurodegeneration but instead repositions it as one pathway among several. This distinction preserves the validity of existing neurodegenerative models while expanding the conceptual space to include non-degenerative and potentially reversible conditions.

9.5. Clinical and Conceptual Implications

The reinterpretation proposed in this manuscript has several important implications. From a clinical perspective, it supports a more nuanced approach to prognosis, in which uncertainty and variability are explicitly acknowledged. This may reduce the risk of premature or overly deterministic prognostic framing, particularly in patients with multifactorial or non-degenerative presentations. From a research perspective, the NOx Framework highlights the need to move beyond single-pathway models and to investigate autonomic dysfunction as a systems-level phenomenon. This includes greater attention to interaction effects, longitudinal variability, and the conditions under which recovery or stabilisation may occur. From a conceptual standpoint, the framework contributes to a broader shift in medicine toward complexity-aware models of disease, in which linear causality is supplemented by network-based and adaptive systems perspectives.

9.6. Limitations

This study is based on a single longitudinal case and an interpretive synthesis of existing literature. As such, it does not provide population-level evidence and should not be interpreted as establishing causal relationships. The purpose of the case is illustrative rather than representative, demonstrating the plausibility of non-degenerative trajectories rather than their prevalence. In addition, while the literature reviewed supports variability in autonomic outcomes, further empirical research is required to define the mechanisms, predictors, and relative frequencies of different trajectories. The NOx Framework should therefore be understood as a hypothesis-generating model rather than a definitive explanatory system.

9.7. Future Directions

Future research should aim to systematically investigate autonomic dysfunction across different aetiologies using longitudinal designs capable of capturing non-linear trajectories. Particular attention should be given to identifying markers of system resilience, recovery potential, and transition between pathways. In addition, greater clarity in terminology is required to distinguish between heterogeneous forms of autonomic dysfunction and specific neurodegenerative conditions. Such clarification would reduce conceptual ambiguity and support more accurate clinical communication. Finally, the integration of systems biology approaches, including network modelling and multi-domain physiological assessment, may provide a more comprehensive understanding of autonomic regulation and its disruption.

9.8. Conclusion of Discussion

The interpretation of autonomic neuropathy as an inherently neurodegenerative condition represents a historically grounded but incomplete model. By integrating longitudinal case evidence with contemporary literature, this manuscript demonstrates that autonomic dysfunction is better understood as a heterogeneous and dynamic phenomenon with multiple potential trajectories.

The NOx (Knox) Framework provides a structured alternative that accommodates this complexity while remaining consistent with established knowledge. In doing so, it offers a more balanced and clinically relevant understanding of autonomic neuropathy, one that recognises progression as a possibility, but not as a certainty.

10. Conclusion

Autonomic neuropathy represents a spectrum of conditions arising from interacting physiological processes rather than a singular disease trajectory. The NOx Framework provides a more comprehensive model by recognising multiple causes and outcomes, thereby challenging deterministic assumptions and supporting a more balanced understanding of autonomic dysfunction. Rather than treating chronic autonomic instability as a phenotype that automatically implies neurodegenerative progression, the evidence assembled in this manuscript supports a distinction between observable presentation and underlying pathway. This distinction is essential for prognosis, for clinical communication, and for the interpretation of cases in which dysautonomia persists without phenoconversion.

The longitudinal case integrated here demonstrates that chronic autonomic dysfunction may remain variable, adaptive, and non-linear over extended periods without evolving into an overt neurodegenerative syndrome. When viewed alongside historical analysis and contemporary dysautonomia literature, this finding reinforces the need to move beyond single-trajectory interpretations and toward a model that better reflects heterogeneity, resilience, and systems interaction. Accordingly, autonomic dysfunction is better understood as a dynamic and multi-pathway process, within which neurodegeneration is one important possibility but not the default or inevitable outcome. The NOx Framework offers a conceptual basis for this reinterpretation and provides a platform for future hypothesis-driven investigation into the mechanisms, trajectories, and prognostic implications of dysautonomia.

➢ **Alignment with Contemporary Dysautonomia Literature (2022–2026): Convergence with Multi-Pathway Models**

Recent advances in the understanding of dysautonomia provide strong empirical support for the reinterpretation of autonomic neuropathy proposed within the NOx (Knox) Framework. Contemporary literature increasingly characterises dysautonomia not as a singular disease entity, but as a heterogeneous spectrum of disorders arising from multiple interacting mechanisms, with clinical trajectories that are variable and frequently non-linear [1,3,10]. This shift reflects a broader movement within autonomic research away from deterministic and structurally anchored models toward systems-based interpretations that emphasise regulatory instability, adaptability, and context-dependent outcomes.

- **Dysautonomia as a Spectrum Disorder**

Modern clinical frameworks define dysautonomia as encompassing a wide range of conditions, including postural orthostatic tachycardia syndrome, neurogenic orthostatic hypotension, autonomic neuropathies, and post-viral autonomic syndromes [1,3,10]. Although these conditions differ significantly in their underlying mechanisms, they share a common feature of impaired autonomic regulation. Recent literature further emphasises that dysautonomia may arise from diverse upstream processes. These include neurodegenerative pathology, such as synucleinopathies, which represent one well-established pathway [4,5]. In addition, immune-mediated and autoimmune mechanisms have been identified as important contributors, particularly in cases of autoimmune autonomic dysfunction [9]. Post-infectious syndromes, including those following viral illness, have also been increasingly recognised as a significant source of autonomic dysregulation [10]. Cardiovascular and baroreflex dysfunction provide another pathway through which autonomic instability may develop, while functional and regulatory disturbances may occur in the absence of identifiable structural damage [6,7,1,10]. Taken together, these observations demonstrate that dysautonomia reflects a system-level disturbance arising from multiple interacting mechanisms, rather than a condition that can be reduced to a single pathological pathway.

- **Post-Viral and Immune-Mediated Pathways**

A major development in recent years has been the recognition of post-viral dysautonomia, particularly in the context of COVID-19 and related syndromes. Studies published from 2022 onward have shown that autonomic dysfunction may persist following acute infection, often without evidence of structural neurological damage [10]. These post-viral presentations are commonly characterised by orthostatic intolerance, abnormalities in heart rate variability, and fluctuating symptom profiles. Importantly, many patients demonstrate partial or gradual recovery over time, further distinguishing these conditions from classical neurodegenerative disorders. Such findings directly challenge earlier assumptions that persistent autonomic dysfunction necessarily reflects progressive neurological degeneration. Instead, they support a model in which prolonged regulatory instability within autonomic networks can occur independently of structural pathology.

- **Divergent Clinical Trajectories**

Contemporary longitudinal studies highlight that dysautonomia exhibits multiple potential clinical trajectories rather than a single progressive course. In some cases, particularly those associated with neurodegenerative disease, a pattern of progressive decline is observed [4,5]. However, other patients demonstrate stabilisation with persistent symptoms over extended periods [6,7]. In addition, fluctuating or relapsing-remitting patterns have been widely documented, particularly in post-viral and functional forms of dysautonomia [10]. Importantly, partial or complete recovery has also been reported, especially in immune-mediated and post-infectious cases [9,10]. This variability in clinical trajectory is now widely recognised within the literature and directly contradicts deterministic interpretations of autonomic neuropathy as an inevitably progressive condition. Instead, it supports a model in which outcomes are dependent on underlying mechanisms, system resilience, and the interaction of multiple physiological factors.

- **Autonomic Regulation as a Systems Phenomenon**

Recent research increasingly conceptualises autonomic function as part of an integrated regulatory network involving cardiovascular, immune, metabolic, and central nervous system processes [1,3,10]. Within this framework, dysautonomia is understood as an emergent property of system-level dysregulation rather than the consequence of isolated neural damage. This perspective is supported by evidence demonstrating interaction between immune

activation and autonomic signalling pathways, particularly in inflammatory and post-infectious conditions [9,10]. In addition, the close coupling between cardiovascular and autonomic systems in the regulation of orthostatic responses has been well established [6,7]. Central-peripheral integration within autonomic control networks further reinforces the view that autonomic function is governed by distributed and interacting systems rather than a single anatomical locus [3–5]. These findings collectively support the interpretation of dysautonomia as a dynamic and adaptive process, consistent with the NOx Framework's emphasis on system-level instability and interaction.

- **Implications for the NOx Framework**

The contemporary dysautonomia literature provides strong external validation for the core propositions of the NOx Framework. It demonstrates that autonomic dysfunction arises from multiple interacting pathways rather than a single disease process [1,3,10]. It also confirms that clinical trajectories are heterogeneous and non-linear, encompassing stabilisation, fluctuation, recovery, and progression [6,7,9,10]. Furthermore, neurodegenerative processes are shown to represent only a subset of dysautonomic conditions rather than their defining feature [4,5]. Finally, the literature supports the interpretation of autonomic dysfunction as a manifestation of system-level instability, consistent with a regulatory network model [3,10]. Taken together, these insights reinforce the argument that autonomic neuropathy should not be interpreted as inherently neurodegenerative, but rather as part of a broader spectrum of dysautonomic conditions with diverse mechanisms and outcomes.

- **Section Conclusion**

The evolution of dysautonomia research between 2022 and 2026 demonstrates a clear and sustained shift toward multi-pathway, systems-based models of autonomic dysfunction. This shift aligns closely with the NOx Framework and provides contemporary empirical support for its reinterpretation of autonomic neuropathy. Accordingly, autonomic dysfunction is best understood as a dynamic, multi-factorial condition with divergent trajectories, rather than a deterministic precursor to neurodegenerative disease.

Reframing Autonomic Dysfunction — From Assumption to Framework

The interpretation of chronic autonomic dysfunction as a predominantly neurodegenerative process has shaped both clinical reasoning and patient expectation for several decades. However, as the preceding analysis demonstrates, this interpretation may reflect historical convergence of terminology and observational bias rather than a universal biological reality. To clarify this position and support the transition toward the Knox (NOx) Framework, three appendices are provided to systematically unpack the evolution of understanding and introduce a revised conceptual model.

First, Appendix 1 examines the historical foundations that led to the widespread assumption that autonomic neuropathy represents a single-pathway, progressive neurodegenerative condition. It demonstrates how early descriptive medicine, combined with later neurodegenerative research paradigms, contributed to a model that emphasised progression while under-recognising variability and recovery.

Second, Appendix 2 addresses a critical source of conceptual ambiguity: the terminological overlap between autonomic neuropathy and pure autonomic failure. It shows how inconsistent use of these terms blurred distinctions between heterogeneous, potentially reversible conditions and defined neurodegenerative disorders, reinforcing a unified but incomplete disease narrative.

Third, Appendix 3 introduces the concept of multifactorial secondary dysautonomia, providing a systems-based explanation for complex autonomic presentations arising from interacting physiological insults, including infection, cardiovascular compromise, surgical intervention, and gastrointestinal dysfunction.

Taken together, these appendices establish the intellectual basis for the Knox Framework Hypothesis: that autonomic dysfunction represents a dynamic, multi-factorial system with divergent trajectories, rather than a condition governed by a single inevitable outcome. This reframing allows for the emergence of dual pathways, progression and recovery, both of which are explored within the Knox Framework and its predictive extensions.

Appendix 1 — Historical Foundations of the Misunderstanding of Autonomic Neuropathy as a Predominantly Neurodegenerative Condition

- **Purpose and Context**

This appendix examines the historical and conceptual development that led to a widely held understanding within medical circles that autonomic neuropathy, particularly when presenting as chronic orthostatic hypotension and multisystem dysautonomia, was predominantly neurodegenerative in nature and associated with a single progressive outcome.

This interpretation did not arise from a single error, but rather from a convergence of clinical observation, limited mechanistic insight, and evolving terminology, which collectively shaped diagnostic thinking over several decades.

- **Early Clinical Descriptions: Phenomenology Before Mechanism**

The earliest descriptions of autonomic dysfunction were grounded in clinical phenomenology rather than pathophysiological distinction. Bradbury and Eggleston described cases of persistent postural hypotension without clear cause, thereby identifying a syndrome defined primarily by orthostatic blood pressure instability rather than underlying mechanism [13].

At that stage, the condition was characterised as idiopathic orthostatic hypotension, there was no clear differentiation between peripheral and central causes, and prognosis and trajectory were largely unknown. These early observations established a clinical pattern without mechanistic resolution, setting the foundation for later interpretive ambiguity [2].

- **Expansion of the Concept: The Rise of "Autonomic Neuropathy"**

As autonomic disorders became more widely recognised, the term "autonomic neuropathy" emerged as a broad descriptor encompassing a range of conditions involving autonomic dysfunction [2]. This term was applied across multiple contexts, including diabetic autonomic neuropathy, acute autonomic neuropathies that were often immune-mediated, chronic idiopathic autonomic dysfunction, and peripheral nerve degeneration affecting autonomic fibres [8,9].

Importantly, the term functioned as a descriptive umbrella rather than a precise diagnostic category. This broad application contributed to an implicit assumption that widespread autonomic dysfunction reflected structural nerve damage and therefore implied a progressive pathological process [1].

- **Lack of Distinction Between Peripheral and Central Autonomic Disorders**

A critical limitation in early and mid-stage literature was the incomplete differentiation between peripheral autonomic neuropathies and central neurodegenerative autonomic failure [2,3]. Patients presenting with orthostatic hypotension, gastrointestinal dysmotility, and cardiovascular instability could represent peripheral neuropathic processes, such as diabetic or autoimmune disease, or central neurodegenerative conditions, including what is now recognised as pure autonomic failure or related synucleinopathies [4,5,8,9]. However, these distinctions were not consistently made. As a result, clinically similar presentations were grouped together, prognostic differences were not clearly recognised, and a uniform trajectory of progression was often assumed [3].

- **Reclassification and the Emergence of Pure Autonomic Failure**

Over time, what had been described as idiopathic orthostatic hypotension was reclassified as pure autonomic failure, a condition now understood to be associated with alpha-synuclein deposition and neurodegenerative processes [12,4]. This represented an important advance in mechanistic understanding. However, this reclassification also had unintended consequences. The clinical presentation of orthostatic hypotension became increasingly associated with neurodegeneration, and the distinction between degenerative and non-degenerative causes was not always clearly maintained in clinical interpretation [3,5]. Thus, the phenotype became linked to a specific pathology, even when that pathology was not universally present.

- **Influence of Neurodegenerative Paradigms**

As research into Parkinson disease, multiple system atrophy, and dementia with Lewy bodies expanded, autonomic dysfunction became recognised as an early or prodromal feature of neurodegenerative disease [4,5]. This further reinforced the association between chronic autonomic dysfunction and progressive neurodegenerative outcomes. In particular, persistent neurogenic orthostatic hypotension, gastrointestinal dysmotility, and bladder dysfunction were increasingly interpreted as indicators of underlying synucleinopathy [4]. This contributed to a broader clinical mindset in which multisystem autonomic dysfunction, especially when persistent, was likely to be degenerative in origin [3].

- **Consolidation of a Single-Trajectory Model**

Through the combined influence of early descriptive ambiguity, the broad use of the term "autonomic neuropathy", the reclassification of idiopathic cases as pure autonomic failure, and expanding neurodegenerative research, a single-trajectory model emerged [2,12,13]. In this model, autonomic dysfunction came to be conceptualised as following a path from instability to chronic progression and ultimately to neurodegenerative outcome [4,5]. Although this model was valid for certain conditions, it was overgeneralised to encompass a wider range of presentations [3].

- **Consequences of This Interpretation**

The adoption of this implicit model led to several important consequences. First, diagnostic bias emerged, whereby clinicians interpreted complex autonomic presentations as inherently progressive even when alternative explanations were possible [1]. Second, prognostic assumptions were shaped by a degenerative lens, influencing expectations and management in patients with multifactorial or potentially reversible conditions [3]. Third, the framework did not adequately accommodate recovery, stabilisation, or mixed and fluctuating trajectories [10].

- **Emerging Evidence Challenging the Model**

Subsequent research has demonstrated that autonomic dysfunction can arise in contexts that are post-viral, immune-mediated, post-surgical or haemodynamic, including cardiac tamponade, and gastrointestinal and vagal in origin, including gastroparesis [9,10,14,15]. In these contexts, symptoms may improve or stabilise, trajectory is not uniformly progressive, and mechanisms differ substantially from neurodegenerative disease [1,10]. This body of evidence challenges the assumption of a single inevitable outcome.

- **Relevance to the Knox (NOx) Framework**

The historical misunderstanding outlined in this appendix provides the conceptual foundation for the development of the Knox Framework. Specifically, it explains why progression has been overemphasised, highlights the absence of a model that accommodates multiple trajectories, and justifies the introduction of multifactorial secondary dysautonomia and a dual-pathway hypothesis encompassing both recovery and progression.

- **Conceptual Reframing**

This appendix supports a fundamental shift. Autonomic dysfunction should not be understood as a condition with a single trajectory, but as a dynamic system with multiple possible outcomes [1,3,10].

- **Conclusion**

The historical conflation of autonomic neuropathy with neurodegenerative autonomic failure reflects the evolution of medical understanding rather than a definitive biological truth.

While neurodegenerative processes remain critically important, they represent one pathway among several rather than the universal endpoint. Recognising this distinction allows for more accurate interpretation of clinical presentations, inclusion of recovery and stabilisation within the model, and development of predictive frameworks that better reflect real-world complexity.

Appendix 2 — Terminological Convergence: Autonomic Neuropathy vs Pure Autonomic Failure

- **Introduction**

A key source of conceptual confusion arose from the interchangeable or overlapping use of terminology, particularly between autonomic neuropathy and pure autonomic failure. These terms, while distinct in modern understanding, were historically used inconsistently, contributing to diagnostic and prognostic ambiguity [2,12].

- **Autonomic Neuropathy as a Non-Specific Descriptor**

The term autonomic neuropathy has historically been used as a broad descriptor for dysfunction of autonomic nerves across multiple aetiologies. These include metabolic conditions such as diabetes, immune-mediated processes, infectious causes, and idiopathic presentations [8,9]. Importantly, many of these conditions are non-degenerative in nature and may demonstrate partial reversibility or long-term stabilisation [1]. Consequently, the use of this term without mechanistic qualification has contributed to conceptual ambiguity in both diagnosis and prognosis [2].

- **Pure Autonomic Failure as a Specific Neurodegenerative Entity**

In contrast, pure autonomic failure is now recognised as a specific neurodegenerative disorder characterised by progressive degeneration of autonomic pathways and associated with alpha-synuclein deposition [12,4]. Clinically, it presents with neurogenic orthostatic hypotension and progressive autonomic impairment [6]. The distinction between this condition and broader categories of autonomic neuropathy is therefore both mechanistically and prognostically significant [3].

- **Historical Overlap and Misinterpretation**

Earlier literature often failed to clearly separate idiopathic autonomic dysfunction from neurodegenerative autonomic failure [2,3]. As a result, patients with non-degenerative or multifactorial conditions were sometimes interpreted within a degenerative framework. Terminology therefore reinforced the perception of inevitable progression and contributed to the development of a unified but incomplete disease narrative [3,5].

- **Impact on Clinical Reasoning**

This convergence led to overestimation of neurodegenerative risk in patients presenting with autonomic dysfunction [1]. It also contributed to under-recognition of reversible or multifactorial conditions and limited the development of conceptual models capable of accommodating recovery or stabilisation [10].

- **Resolution in Contemporary Understanding**

Modern research increasingly distinguishes peripheral and autonomic neuropathies, which are heterogeneous and often non-progressive, from pure autonomic failure and related synucleinopathies, which are progressive neurodegenerative disorders [3–5,12]. This distinction is foundational to the Knox Framework's reinterpretation of autonomic dysfunction.

Appendix 3 — Introduction of Multifactorial Secondary Dysautonomia

- **Conceptual Introduction**

The concept of multifactorial secondary dysautonomia represents a critical shift from single-cause models toward systems-based understanding. It recognises that autonomic dysfunction may arise from multiple interacting insults rather than a single pathological driver.

- **Contributing Factors**

Autonomic dysfunction may arise from a range of interacting contributing factors rather than one discrete cause. Infectious triggers, particularly post-viral syndromes, are increasingly recognised as a source of autonomic dysregulation [10]. Cardiovascular events, such as cardiac tamponade, can disrupt haemodynamic stability and impair autonomic control [14]. Surgical trauma, including major procedures such as open-heart surgery, may alter autonomic signalling and baroreflex function [6]. Gastrointestinal dysregulation, as observed in conditions such as gastroparesis, reflects dysfunction within vagal and enteric pathways [15].

Each of these factors may contribute independently or in combination to the development of autonomic instability [1].

- **Systems Interaction**

These factors interact across central autonomic networks, peripheral nerves, cardiovascular regulation, and gastrointestinal motility [3,6]. The resulting state is therefore better understood as a compound physiological burden arising from system-level interaction rather than a single focal lesion [1].

- **Clinical Implications**

Multifactorial dysautonomia may mimic neurodegenerative disease and may present with severe instability. However, it does not necessarily follow a progressive trajectory. The appearance of severity at presentation does not, in itself, establish an underlying degenerative mechanism.

- **Divergent Outcomes**

From this systems-based perspective, autonomic dysfunction may follow divergent clinical trajectories. One pathway is characterised by recovery, involving neural adaptation, physiological compensation, and gradual stabilisation of function [10]. Another pathway involves progression, in which persistent dysregulation, and in some cases structural degeneration, leads to worsening instability [4,5]. The distinction between these pathways is not predetermined by presentation alone, but is influenced by the interaction of underlying mechanisms, cumulative stressors, and

system resilience [3].

- **Integration into the Knox Framework**

This concept underpins the dual-pathway hypothesis within the Knox Framework. The outcome is not predetermined by the initial phenotype, but emerges from the interaction of contributing factors and adaptive capacity. This framework therefore allows for progression in some cases and recovery or stabilisation in others.

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Conflicts of Interest

The author declares no conflicts of interest.

Ethics Statement

This manuscript presents a self-reported longitudinal case integrated with literature analysis. No institutional ethical approval was required.

Consent

The author is the subject of the case described and consents to publication.

Data Availability

All relevant data are contained within this manuscript.

Disclaimer

This work is presented as a hypothesis and interpretive analysis and does not constitute medical advice.

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