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Review Article

Amyotrophic Lateral Sclerosis (ALS) and the Inflammatory Axis: A Functional Model for Intervention and Management

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressive and ultimately fatal neurodegenerative disorder marked by the selective loss of upper and lower motor neurons. Despite decades of research, conventional treatments remain limited to symptom management and modest extensions of survival, with no therapies capable of altering the disease's fundamental trajectory. Recent advances in molecular neurobiology have highlighted the critical role of chronic neuroinflammation, oxidative stress, mitochondrial failure, and neuroendocrine disruption as central, interlinked drivers of ALS pathogenesis. These discoveries demand a paradigm shift toward a system-based, personalized therapeutic model.

This paper introduces a comprehensive clinical strategy developed by Millennium Health Centers, built around a 28-point biomarker panel designed to detect subtle imbalances across inflammatory, oxidative, hormonal, and metabolic domains. By leveraging this diagnostic insight, the Millennium Protocol guides the application of precision nutraceuticals to downregulate pro-inflammatory cytokines and reactive oxygen species, alongside bioidentical hormone replenishment to restore neurosteroid balance and hypothalamic-pituitary axis integrity. Together, these interventions aim to reestablish systemic and neuronal homeostasis, mitigate ongoing neurodegeneration, and meaningfully enhance function and quality of life for individuals affected by ALS. This integrative approach represents a promising frontier in ALS care and warrants broader investigation through observational and interventional trials.

***Keywords**: Neuroinflammation; Peroxynitrite; Pregnenolone; DHEA; IGF-1*

Introduction

While Amyotrophic Lateral Sclerosis (ALS) is classically categorized as a motor neuron disease, compelling evidence now supports the view that its root pathology lies in chronic, unchecked neuroinflammation [1]. This inflammation is orchestrated primarily by activated microglia and reactive astrocytes, which propagate a toxic cascade involving pro-inflammatory cytokines (e.g. IL-1β, TNF-α, IL-6), reactive oxygen (ROS) and nitrogen species (RNS), and excitotoxic glutamate release (Figure 1). These processes collectively disrupt synaptic signaling, compromise blood-brain barrier integrity, and directly induce motor neuron apoptosis [2].

Crucially, neuroinflammation in ALS is not merely a downstream consequence of neuronal loss, it precedes and accelerates neurodegeneration. Genetic and experimental models consistently demonstrate that glial-derived inflammation, particularly through NF-κB, NADPH oxidase, and NLRP3 inflammasome pathways, initiates mitochondrial dysfunction, protein misfolding, and axonal transport deficits well before overt symptom onset [3]. Furthermore, this inflammatory state disrupts neuroendocrine signaling, notably the hypothalamic-pituitary-adrenal (HPA) axis, leading to reductions in key neuroprotective hormones such as pregnenolone, DHEA, and testosterone. This hormonal collapse further impairs neuronal resilience and metabolic integrity [4].

The Millennium Protocol offers a novel systems-based approach to ALS, centered on identifying and correcting these neuroinflammatory and neuroendocrine disruptions. Through the use of a 28-point biomarker panel, the protocol enables precise characterization of each patient's inflammatory and hormonal landscape. Interventions are then tailored using evidence-based nutraceuticals and bioidentical hormone replenishment to restore homeostasis, with the ultimate goal of slowing disease progression and improving neurological function and quality of life [5].

The role of neuroinflammation in ALS

Chronic neuroinflammation is increasingly recognized as a principal driver-not merely a byproduct-of motor neuron degeneration in Amyotrophic Lateral Sclerosis (ALS). Elevated concentrations of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) are consistently found in the cerebrospinal fluid and peripheral blood of ALS patients, often correlating with disease severity and progression rates [6].

Central to this inflammatory axis is the persistent activation of microglia, the resident immune cells of the central nervous system. In ALS, microglia undergo a phenotypic shift toward a pro-inflammatory M1 state, characterized by the release of nitric oxide (NO), superoxide, and other reactive oxygen species (ROS). These free radicals inflict oxidative damage on lipid membranes, proteins, and mitochondrial DNA, hastening motor neuron apoptosis [7].

Astrocytes, which ordinarily support neuronal health and glutamate clearance, become dysfunctional and lose their neuroprotective phenotype. Instead, they contribute to glutamate excitotoxicity-a pathological accumulation of glutamate that overstimulates NMDA and AMPA receptors, leading to calcium influx, mitochondrial overload, and cell death.

Further amplifying this destructive cycle is the activation of intracellular signaling pathways such as NF-κB and the NADPH oxidase complex. These pathways generate peroxynitrite ($ONOO^-$), a highly reactive nitrating species formed from NO and superoxide. Peroxynitrite modifies proteins via tyrosine nitration, denatures important enzyme pathways, disrupts mitochondrial respiration, impairs axonal transport, and compromises DNA repair mechanisms-all culminating in progressive motor neuron degeneration [8].

This chronic neuroinflammatory environment not only injures neurons directly but also perpetuates endocrine dysfunction, glial scarring, and immunoexcitotoxicity. Addressing this inflammatory cascade is therefore a foundational strategy in the Millennium Protocol, aiming to intercept and downregulate the upstream mechanisms fueling ALS pathogenesis [9,10].

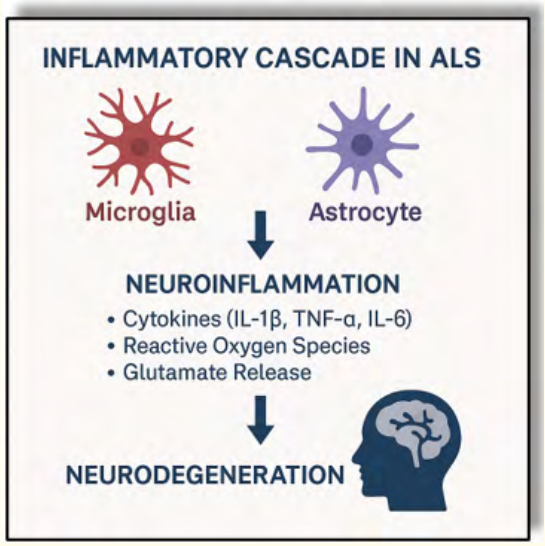

Figure 1

Trauma as a precipitating factor in ALS: Linking injury to neurodegeneration

Research indicates that a significant proportion of individuals diagnosed with amyotrophic lateral sclerosis (ALS) have a history of physical trauma, particularly head injuries [11-13]. A comprehensive meta-analysis encompassing 29 studies with over 18,000 ALS cases and more than 6.5 million controls found that individuals with a history of trauma had a 51% increased risk of developing ALS compared to those without such a history (pooled odds ratio [OR] = 1.51; 95% confidence interval [CI]: 1.32-1.73) [14-16].

Specifically, the association between head trauma and ALS was notable. One study reported that individuals with a history of head injury had a 70% increased risk of developing ALS (OR = 1.7; 95% CI: 1.3-2.2) [17].

Furthermore, the timing and frequency of traumatic events appear to influence ALS risk. Trauma occurring within five years prior to ALS diagnosis was associated with an 84% increased risk (OR = 1.84; 95% CI: 1.56-2.17). Repeated traumatic events also elevated risk, with individuals experiencing multiple traumas showing a 21% increased risk (OR = 1.21; 95% CI: 1.07-1.38) [18,19].

Just for clarity, while trauma is not the sole cause of ALS, these findings suggest that a history of physical trauma, especially head injuries, may contribute to an increased risk of developing the disease.

Neuroendocrine dysregulation in ALS

Neuroendocrine dysfunction is an underrecognized but central feature in ALS, contributing to both symptom burden and disease progression. ALS patients frequently exhibit suppressed levels of critical neurosteroids and anabolic hormones-including pregnenolone, DHEA, testosterone (free and total), and thyroid hormones-while often displaying elevated cortisol and disrupted feedback within the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes [20]. These imbalances are not coincidental; they represent an endocrine fingerprint of chronic neuroinflammatory suppression.

Neuroinflammation, a hallmark of ALS pathology, interferes with hypothalamic regulation of gonadotropin-releasing hormone (GnRH), leading to reduced pituitary output of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [21]. This cascade directly diminishes testicular and adrenal production of testosterone, estradiol, DHEA, and progesterone. Concurrently, elevated inflammatory cytokines (e.g. IL-6, TNF-α) upregulate type 3 deiodinase, shunting thyroid hormone conversion toward inactive reverse T3 and contributing to intracellular hypothyroidism despite normal serum TSH or free T4 levels [22].

The consequences of this hormonal collapse are profound. Pregnenolone and progesterone, both precursors in the steroidogenic cascade, have powerful anti-inflammatory, neuroprotective, and mitochondrial stabilizing effects [23]. Their depletion removes a crucial layer of defense against excitotoxicity, oxidative stress, and glial overactivation. Testosterone and DHEA further modulate inflammatory signaling, improve synaptic plasticity, and support energy metabolism. When these are deficient, mitochondrial function is impaired, and neuronal vulnerability increases.

IGF-1, often suppressed in ALS due to chronic illness, neuroinflammation, malnutrition, or disrupted growth hormone signaling (due to elevated cortisol), is another critical factor [24]. It promotes neurogenesis, supports oligodendrocyte function, and enhances remyelination. Low IGF-1 correlates with faster disease progression and reduced regenerative capacity in motor neurons.

Additionally, dysregulation of thyroid hormones, particularly low free T3 and elevated reverse T3, leads to metabolic slowing at the cellular level, reducing ATP production, impairing thermoregulation, and worsening neurocognitive function [25]. This state of "cellular hypothyroidism" is frequently missed in conventional testing but is a common finding in ALS patients assessed using the Millennium Protocol.

Together, these hormonal disturbances form a self-perpetuating loop: neuroinflammation suppresses endocrine output, which in turn removes the neurosteroid brakes on inflammation and repair. Breaking this cycle, by identifying and correcting neuroendocrine deficits, represents a key therapeutic strategy. The Millennium 28, Point Biomarker Panel offers clinicians a structured framework to diagnose these dysfunctions and guide targeted, evidence, based hormone restoration protocols aimed at improving resilience, slowing progression, and enhancing quality of life in ALS patients.

The millennium 28-point biomarker panel

The Millennium 28-Point Biomarker Panel is a systems-level diagnostic tool designed to detect subtle neuroendocrine and biochemical dysfunctions, particularly in conditions characterized by chronic inflammation, trauma, and neurodegeneration such as ALS. Unlike traditional lab panels, which interpret biomarkers in isolation, the Millennium panel evaluates dynamic interrelationships among neurosteroids, pituitary-derived hormones, metabolic regulators, and essential micronutrients [26,29].

The panel includes measurement of pregnenolone, DHEA, DHEA-sulfate, progesterone, estradiol, estrone, total testosterone, free testosterone, dihydrotestosterone (DHT), sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, insulin, insulin-like growth factor-1 (IGF-1), growth hormone (GH), vitamin D (25-hydroxy), zinc, TSH, free T3, free T4, reverse T3, T3/rT3 ratio, and thyroid peroxidase antibodies (TPO-Ab). Additional calculations include the TSH index (Jostel's Index), offering insight into pituitary responsiveness to circulating thyroid hormone levels [27].

This panel is particularly adept at identifying pleiotropic hormones with anti-inflammatory and neuroprotective effects. Pregnenolone, for example, suppresses microglial activation and enhances GABAergic tone, while progesterone is a known precursor to allopregnanolone, a neurosteroid that downregulates pro-inflammatory cytokines such as TNF-α and IL-1β and modulates GABA-A receptor sensitivity. DHEA and DHEA-S not only support the synthesis of downstream androgens and estrogens but also inhibit NF-κB signaling, attenuate IL-6 production, and exert mitochondrial protective effects. Estradiol has well-documented anti-inflammatory actions through modulation of

microglial reactivity and enhancement of BDNF signaling, while testosterone directly inhibits TNF-α and protects against excitotoxicity in CNS models [28].

Thyroid markers-particularly free T3 and reverse T3-offer insight into metabolic and mitochondrial efficiency. Inflammatory stress or toxin exposure often leads to increased conversion of T4 into inactive reverse T3, a process identified as low T3 syndrome, which suppresses ATP production and exacerbates neuronal decline. Simultaneously, low free T3 in the setting of normal TSH and free T4 may indicate cellular hypothyroidism, especially prevalent in post-traumatic or neuroinflammatory states.

Insulin is also measured not just as a metabolic marker, but as a neuromodulator influencing central glucose uptake, neurotransmitter synthesis, and inflammation. Chronic hyperinsulinemia, even in normoglycemic individuals, can suppress SHBG, reduce testosterone bioavailability, and interfere with deiodinase function, worsening thyroid hormone conversion.

Micronutrients such as vitamin D and zinc are critical immunomodulators. Vitamin D regulates T-regulatory cell activity, downregulates IL-17, and protects the CNS from autoimmune insult, while zinc is indispensable for testosterone production, glutamate balance, and inhibition of NF-κB-a central inflammatory pathway in ALS.

By evaluating these 28 biomarkers in context, the Millennium Protocol can detect early patterns of neuroimmune dysregulation, guide hormone restoration therapy, and provide targeted anti-inflammatory nutraceutical interventions. This model is essential for reversing the downstream effects of neuroinflammation, restoring endocrine feedback loops, and optimizing neuronal survival in complex conditions like ALS.

Interpretive integration of the millennium 28-point biomarker panel

Due to the complex biochemical and neuroendocrine interactions inherent in the 28 biomarkers evaluated within the Millennium Panel, a proprietary expert AI platform was developed over a 10-year period to perform advanced cross-correlational analysis. This system-trained on thousands of clinical cases and validated by iterative clinical feedback-allows for dynamic interpretation of results across multiple physiological axes, including neuroinflammation, hypothalamic-pituitary-adrenal (HPA) function, thyroid conversion efficiency, gonadal regulation, mitochondrial capacity, and micronutrient status.

Unlike conventional laboratory assessments that rely on static reference ranges and single-axis evaluation, the AI-driven model evaluates the biochemical "language" spoken among biomarkers-identifying compensatory mechanisms, suppressed pathways, and pattern-based abnormalities that would otherwise remain undetected. The system can flag suspected medical conditions such as pituitary micro- or macroadenomas, central hypothyroidism, insulin resistance, subclinical autoimmunity, or steroidogenic collapse-often before they manifest in overt clinical disease [26].

In addition to differential diagnostic suggestions, the AI provides a predictive, personalized treatment protocol. This includes prioritization of hormone restoration, nutraceutical support, detoxification strategies, and further laboratory testing where appropriate. The result is a tailored therapeutic roadmap that targets root dysfunction and adapts dynamically over time, improving precision and outcomes in the management of complex neuroendocrine and neurodegenerative conditions [27].

Hormonal replenishment strategy

The foundation of the Millennium Protocol's hormone replacement strategy is precise biochemical targeting-guided exclusively by abnormalities identified within the 28-point biomarker panel and interpreted in the context of clinical symptomatology. This panel

enables the clinician to predict specific hormonal insufficiencies or imbalances, many of which are not evident through standard screening. It also reveals patterns of neuroinflammatory suppression and neuroendocrine collapse that are characteristic of ALS and other neurodegenerative conditions [28,29].

Treatment is not empirical or generalized; it is individualized, using the biomarker data to select only those hormones and prohormones that are functionally deficient, dysregulated, or insufficiently converted at the tissue level. The therapeutic objective is to restore physiologic concentrations of key regulatory hormones known to have anti-inflammatory, neuroprotective, and mitochondrial-enhancing effects-ultimately improving neuronal resilience and systemic homeostasis.

Pregnenolone and progesterone are frequently the first-line targets in cases of neurosteroid depletion. These two prohormones, both synthesized from cholesterol, are critical for maintaining glial stability and modulating the neuroinflammatory cascade. Clinical restoration of pregnenolone can help reestablish GABAergic tone and acetylcholine synthesis, while progesterone-particularly through its conversion to allopregnanolone-reduces central levels of TNF-α and IL-6, protects oligodendrocytes, and stabilizes the blood-brain barrier [30,31].

DHEA, often deficient in ALS patients due to chronic HPA axis suppression, is another pleiotropic hormone with profound influence on cognition, immune regulation, and mitochondrial energy metabolism. Its replenishment, when guided by lab-confirmed deficiency, has been shown to restore androgen balance, modulate mood, and inhibit NF-κB signaling pathways involved in neurodegeneration [32].

Testosterone replacement, when indicated by low total or free testosterone levels on the panel, supports neuromuscular strength, increases mitochondrial biogenesis, and suppresses pro-inflammatory cytokines such as IL-1β. In ALS patients, testosterone is also essential for preserving lean body mass and counteracting the catabolic effects of chronic inflammation and immobility [33].

Thyroid hormone optimization, particularly of free T3 and free T4, plays a critical role in restoring cellular energy dynamics. The biomarker panel frequently reveals low free T3 or elevated reverse T3, indicating impaired peripheral conversion or cellular hypothyroidism, which contributes to fatigue, cognitive slowing, and metabolic decline. In such cases, T3-containing formulations may be favored over T4-only regimens to bypass conversion blockades and deliver active hormone directly to the cell [34].

IGF-1, a surrogate marker of growth hormone activity, is measured directly in the panel and serves as a reliable indicator of the body's regenerative capacity. In ALS, low IGF-1 is associated with accelerated neuronal atrophy. When deficiency is confirmed, interventions to stimulate endogenous production-through GH secretagogues or, in select cases, rhGH-can support neuronal growth, myelin integrity, and overall neurological recovery [35].

All hormonal therapies are administered using bioidentical formulations, delivered transdermally, sublingually, or via subcutaneous injection, with routes selected to optimize absorption, circadian rhythm alignment, and patient compliance. Treatment is continuously monitored and adjusted based on follow-up biomarker testing and clinical outcomes, ensuring that hormone levels remain within optimal functional ranges and avoiding over-replacement.

By tailoring hormonal replenishment precisely to each patient's biochemical profile, the Millennium Protocol delivers a targeted and dynamic therapeutic approach that addresses the endocrine underpinnings of ALS pathophysiology-bridging the gap between laboratory data and functional neurorestoration.

Nutraceutical intervention strategy

The integrative neuroprotective approach to ALS within this model relies on the use of strategically combined nutraceuticals shown to downregulate neuroinflammation, restore mitochondrial integrity, and mitigate oxidative stress. One critical component of this strategy

includes the long-chain omega-3 fatty acid DHA, which is vital for neuronal membrane fluidity and integrity. DHA-derived resolvins and protectins act as endogenous anti-inflammatory mediators, effectively suppressing cytokine-driven neuroinflammation at the glial interface [36-39].

Tocopherols-specifically alpha, delta, and gamma forms of vitamin E-further contribute by modulating redox-sensitive transcription factors like NF-κB, thereby reducing the transcription of proinflammatory cytokines such as IL-1β and TNF-α. These actions are amplified by the inclusion of ascorbic palmitate, a lipid-soluble antioxidant that enhances blood-brain barrier penetration and assists in glutathione synthesis, providing intracellular protection against peroxynitrite and superoxide radicals [40,41].

Mitochondrial bioenergetics are supported through a combination of coenzyme Q10 and pyrroloquinoline quinone (PQQ) [42]. CoQ10 facilitates electron transport chain efficiency, helping preserve ATP production in energy-demanding tissues such as the brain and spinal cord, while PQQ stimulates mitochondrial biogenesis and the expression of nerve growth factors essential for neuronal survival. This effect is bolstered by the presence of quercetin, which enhances mitochondrial output and blocks inflammatory signaling pathways [43-48].

Further neuroprotection and energy regulation are provided by a tailored B-vitamin complex, including methylcobalamin (B12), thiamine (B1), riboflavin (B2), and pantothenic acid (B5). These cofactors support neurotransmitter synthesis, myelin maintenance, and glucose metabolism, all of which are frequently impaired in ALS. Their inclusion ensures optimal enzymatic activity in redox and methylation cycles critical to neuronal health [49].

Polyphenolic compounds such as epigallocatechin gallate (EGCG) and hesperidin exert additional neurorestorative benefits by enhancing cerebral circulation, reducing excitotoxicity, and modulating expression of BDNF, a key player in neuroplasticity and axonal repair. Rhodiola rosea and guarana extract contribute adaptogenic and stimulatory properties, which counteract fatigue, support stress tolerance, and help restore cognitive clarity in ALS patients [50] (Figure 2).

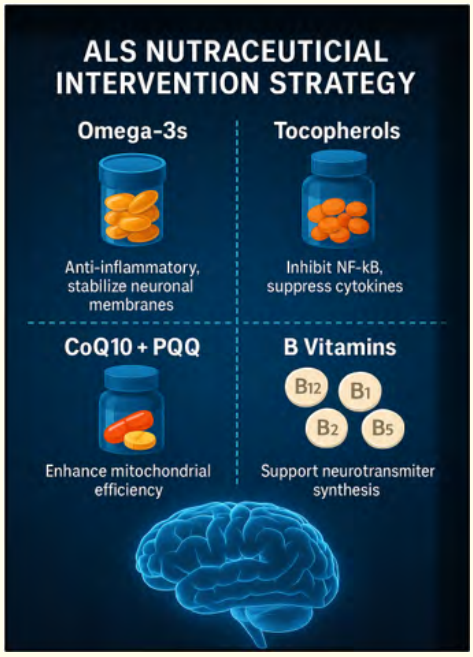

Figure 2

Together, this combination of nutraceutical agents offers a synergistic approach to attenuate neurodegeneration by reducing proinflammatory signaling, optimizing mitochondrial function, enhancing antioxidant defenses, and promoting neuroregenerative processes. This multifactorial intervention addresses not only the pathophysiology of ALS but also improves resilience at both cellular and systemic levels.

Clinical application and outcome tracking

Patients are evaluated at baseline and every 90-180 days with repeat biomarker testing, neurological assessments, and quality-of-life indices (ALSFRS-R, fatigue scales, mood assessments) [51]. Treatment response is tracked using trends in inflammatory cytokines, oxidative stress markers, and hormonal normalization. Adjustments to the protocol are made based on biomarker evolution and clinical trajectory using the Monthly Program Questionnaire (MPQ).

Case Illustration

A 54-year-old male with limb-onset ALS presented with fatigue, muscle atrophy, depression, and low libido. His 28-point panel revealed elevated IL-6, low pregnenolone and testosterone, suboptimal vitamin D, elevated homocysteine, and low CoQ10. He was placed on a protocol including quercetin, PQQ, CoQ10, NAC, omega-3s, vitamin D3/K2, pregnenolone (100 mg), testosterone, and combination T4/T3. Over 6 months, his inflammatory markers normalized, strength stabilized, and quality-of-life scores improved. Though disease progression was not halted, symptom severity decreased, and functional independence was prolonged.

Conclusion

Amyotrophic Lateral Sclerosis is a complex, multisystem disease driven not only by motor neuron loss but by interconnected processes involving neuroinflammation, endocrine collapse, oxidative stress, and mitochondrial dysfunction. Conventional approaches, which narrowly focus on symptom suppression or neuroprotection in isolation, have failed to significantly alter the course of the disease.

The Millennium Protocol offers a fundamentally different therapeutic paradigm-one grounded in systems medicine and precision diagnostics. Through the use of a validated 28-point biomarker panel, clinicians can detect and quantify the underlying biochemical drivers of neurodegeneration with a level of granularity that is not possible through conventional testing. These findings then guide an individualized treatment strategy using bioavailable nutraceuticals to downregulate inflammation and oxidative stress, and bioidentical hormones to replenish neuroprotective and regulatory deficits that are both causative and perpetuating factors in ALS.

While this approach is not yet curative, its capacity to reduce symptom burden, stabilize functional decline, and improve neurological and systemic resilience offers ALS patients a new model of care-one that is proactive, mechanistically informed, and responsive to each patient's unique physiological profile. The consistent patterns identified through the biomarker panel and the measurable clinical responses observed in practice underscore the urgent need for formal observational and interventional studies to validate and expand this promising protocol. In the evolving landscape of neurodegenerative therapeutics, the Millennium Protocol stands as a rational and hopeful framework for altering the trajectory of ALS and restoring lost quality of life.

Closing Thought: "How do you know if it will or will not work if you never try?"

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