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Neuroimmune Regulation in Autoimmune Hemolytic Anemia: A Missing Link in Disease Persistence and Relapse

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Abstract

Autoimmune Hemolytic Anemia (AIHA) is a rare but potentially life-threatening disorder characterized by the immune system's aberrant targeting and destruction of red blood cells (RBCs). Despite advances in diagnostics and immunosuppressive therapies, the disease often follows a relapsing-remitting course, the underlying mechanisms of which remain poorly understood. Emerging research points toward the neuroimmune axis as a key modulator of immune homeostasis, linking nervous system activity to immune cell behavior. The bidirectional communication between the central nervous system (CNS) and peripheral immunity, mediated by neurotransmitters, neuropeptides, and the autonomic nervous system, plays a critical role in orchestrating immune responses. Disruptions in this axis can lead to chronic inflammation, immune dysregulation, and disease relapse. In the context of AIHA, neuroimmune interactions may influence T-cell differentiation, cytokine production, and macrophage activation, all of which are central to the pathophysiology of hemolysis. This review explores the potential involvement of neuroimmune regulation in the persistence and recurrence of AIHA, highlighting mechanisms such as the hypothalamic-pituitary-adrenal (HPA) axis, vagus nerve signaling, and neuroinflammatory pathways. Understanding the neuroimmune crosstalk in AIHA may offer novel insights into disease mechanisms and therapeutic avenues.

1. Introduction

Autoimmune hemolytic anemia (AIHA) is a rare but potentially life-threatening disorder characterized by the destruction of red blood cells (RBCs) due to autoantibodies directed against self-antigens on erythrocyte membranes (Michalak et al., 2020). The disease manifests in a highly heterogeneous clinical spectrum, ranging from mild anemia to severe hemolytic crises with multi-organ complications. Despite advancements in understanding immune dysregulation, the pathogenesis of AIHA remains incompletely elucidated, especially regarding the mechanisms underlying disease persistence and relapse. Conventional models focus predominantly on immune tolerance breakdown, B-cell autoreactivity, and regulatory T-cell dysfunction (Cashman et al., 2019). However, emerging evidence points to a more intricate network involving the central and peripheral nervous systems in modulating immune activity, a concept known as neuroimmune regulation.

Neuroimmune interactions refer to the bidirectional communication between the nervous and immune systems, which occurs via neural, hormonal, and cytokine-mediated signaling (Krsek et al., 2024). This crosstalk plays a critical role in maintaining systemic homeostasis, and its disruption has been implicated in numerous autoimmune and inflammatory diseases, including systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis. In the context of AIHA, the potential contribution of neuroimmune mechanisms especially those influencing immune tolerance, B-cell maturation, and cytokine environments has not yet been fully explored. The autonomic nervous system, particularly the vagus nerve, exerts immunomodulatory effects through what is termed the "inflammatory reflex." The vagus nerve transmits afferent signals from inflammatory sites to the brain, which in turn sends efferent signals that modulate cytokine production, antigen presentation, and leukocyte activity via the cholinergic anti-inflammatory pathway (Bonaz et al., 2016). Such pathways are increasingly recognized for

their role in immune regulation and tolerance induction. Additionally, the hypothalamic-pituitary-adrenal (HPA) axis a key component of neuroendocrine regulation affects immune responses by modulating glucocorticoid release (Bellavance and Rivest, 2014). While corticosteroids remain a frontline treatment for AIHA, the chronic dysregulation of the hypothalamic-pituitary-adrenal axis, particularly in stress conditions, may lead to immune system imbalances that promote disease recurrence or refractoriness to therapy (Lawrence and Scofield, 2024). This highlights the possible feedback loop between psychological stressors, neuroendocrine responses, and autoimmune flares, further emphasizing the need to understand neuroimmune dynamics.

Recent research in psychoneuroimmunology has demonstrated how neural inputs influence the behavior of immune cells within lymphoid organs and the bone marrow niche. In AIHA, where extramedullary hemolysis and compensatory erythropoiesis are active processes, neuroimmune regulation may affect the bone marrow microenvironment and erythropoietic stress responses (Barcellini and Fattizzo, 2020). It is plausible that maladaptive signaling through sympathetic fibers innervating hematopoietic organs could alter antigen presentation, leading to autoantibody generation or persistence. Another critical aspect involves microglial and astrocyte-mediated responses within the CNS, which may contribute to systemic autoimmune activity. Although primarily involved in neuroinflammation, these glial cells secrete cytokines that can have peripheral immunological effects. Neuroinflammation has been shown to impact peripheral immune tolerance and may play a role in exacerbating autoimmune disorders, including AIHA, via a yet unidentified mechanism (Xiang et al., 2023). Furthermore, the emerging field of vagus nerve stimulation therapy, already approved for treatment-resistant epilepsy and depression, has demonstrated promising immunosuppressive effects in inflammatory disorders. This suggests a novel therapeutic avenue in AIHA, particularly for patients with relapsing or steroid-refractory disease, where conventional immunosuppression carries significant long-term toxicity.

2. Neuroimmune Communication Pathways in Autoimmune Regulation

The immune and nervous systems engage in continuous crosstalk through complex neuroimmune pathways involving neurotransmitters, neuropeptides, and cytokines. This bidirectional communication maintains immune homeostasis and ensures a balanced response to stress and inflammation (Kamimura et al., 2020). In the context of autoimmunity, particularly AIHA, these regulatory circuits may become dysregulated, contributing to the breakdown of tolerance. The autonomic nervous system especially the sympathetic and parasympathetic branches modulates immune responses by influencing leukocyte trafficking, cytokine profiles, and lymphoid organ activity (Kenney and Ganta, 2014). Parasympathetic vagal signals, via the cholinergic anti-inflammatory pathway, inhibit pro-inflammatory cytokine release through α7 nicotinic acetylcholine receptors (α7nAChRs) on macrophages (Ulloa, 2005). This neural regulation, known as the inflammatory reflex, may become impaired in chronic autoimmune diseases. Additionally, the hypothalamic-pituitary-adrenal axis regulates systemic immunity via cortisol, which suppresses inflammation and autoimmunity. In AIHA, stress-induced hypothalamic-pituitary-adrenal axis dysregulation may lead to altered glucocorticoid sensitivity, contributing to persistent immune activation despite corticosteroid therapy (Silverman et al., 2005). Furthermore, peripheral immune organs such as the spleen and bone marrow receive sympathetic innervation that influences antigen presentation and immune cell development. Disruptions in these neural inputs could impair the clearance of autoreactive clones or alter erythropoiesis. Recent studies in psychoneuroimmunology emphasize how neuroimmune imbalance contributes to disease chronicity in systemic autoimmunity (Schwab et al., 2014). By examining the autonomic nervous system and hypothalamic-pituitary-adrenal axis in AIHA, researchers can identify novel mechanistic insights into immune persistence, offering a broader perspective that goes beyond classical immunological models. This understanding also opens new possibilities for therapeutic intervention via neuromodulation.

3. Stress, Neuroendocrine Dysregulation, and AIHA Relapse

Psychological and physiological stress can profoundly influence the immune system through neuroendocrine mechanisms, particularly involving the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. In AIHA, recurrent disease flares are often temporally associated with stress events, suggesting a mechanistic link between stress-induced neuroendocrine dysregulation and immune dysregulation. Under stress, the hypothalamic-pituitary-adrenal axis becomes activated, increasing glucocorticoid release (DeMorrow, 2018). While corticosteroids initially suppress inflammation, chronic elevation of cortisol may lead to glucocorticoid receptor desensitization, reducing their immunosuppressive efficacy (Sevilla et al., 2021). This could explain the reduced responsiveness to steroid therapy observed in relapsing AIHA patients.

Moreover, chronic stress alters the balance between pro- and anti-inflammatory cytokines. Increased levels of IL-6, TNF-α, and IFN-γ, often found in AIHA, can be exacerbated by prolonged sympathetic activation (Fattizzo et al., 2020). Sympathetic nerve endings in lymphoid tissues secrete norepinephrine, which can shift T-cell responses towards Th1 and Th17 phenotypes both associated with autoimmunity (Bucsek et al., 2018). These changes foster a pro-inflammatory environment that facilitates the activation of autoreactive B cells and persistence of autoantibodies against red blood cells. Furthermore, stress affects the function of regulatory T cells and antigen-presenting cells, compromising immune tolerance. Stress-induced sleep disruption, circadian rhythm disturbances, and altered melatonin levels can also impair immune checkpoint regulation, contributing to autoantibody

resurgence (Awuah et al., 2023). Understanding these neuroendocrine influences is crucial in managing relapsing AIHA and designing interventions that incorporate stress reduction techniques, behavioral therapy, and neuroendocrine modulators as part of a comprehensive disease management strategy. This perspective advocates for the inclusion of mental health and neurobiology in autoimmune disease care.

4. Central Nervous System Inflammation and Peripheral Autoimmunity

In autoimmune diseases, neuroinflammation can modulate peripheral immunity through multiple routes. In AIHA, microglial activation, astrocyte cytokine release, and disruption of the blood-brain barrier (BBB) may influence systemic immune activity and tolerance (Hauptmann et al., 2020). CNS immune cells, particularly microglia, can release IL-1β, IL-6, and TNF-α, which not only mediate neuroinflammation but also have peripheral immunostimulatory effects, promoting B-cell hyperactivity and antibody production (Yang et al., 2020). The vagus nerve, which connects the brain to visceral organs, including the spleen and bone marrow, plays a critical role in the modulation of peripheral immune responses (Bonaz et al., 2017). CNS inflammation can alter vagal tone, reducing anti-inflammatory output and enhancing systemic inflammation. In AIHA, where immune tolerance is already compromised, these neural alterations may sustain autoantibody production and impair resolution of inflammation. The gut-brain-immune axis is another emerging link, where CNS alterations affect gut microbiota composition and vice versa, further influencing systemic immune regulation. Neuroinflammatory pathways also interfere with hematopoietic niches. CNS-derived stress signals can disrupt bone marrow homeostasis and the function of hematopoietic stem cells, potentially contributing to ineffective erythropoiesis and the persistence of autoreactive clones (Carpenter and Maryanovich, 2024). Therefore, examining CNS-peripheral immune interactions offers an enriched understanding of AIHA pathophysiology. Investigating CNS-targeted therapies, such as anti-inflammatory neuromodulators, BBB stabilizers, or behavioral interventions that reduce neuroinflammation, could open new therapeutic avenues in managing chronic and relapsing autoimmune hemolytic anemia.

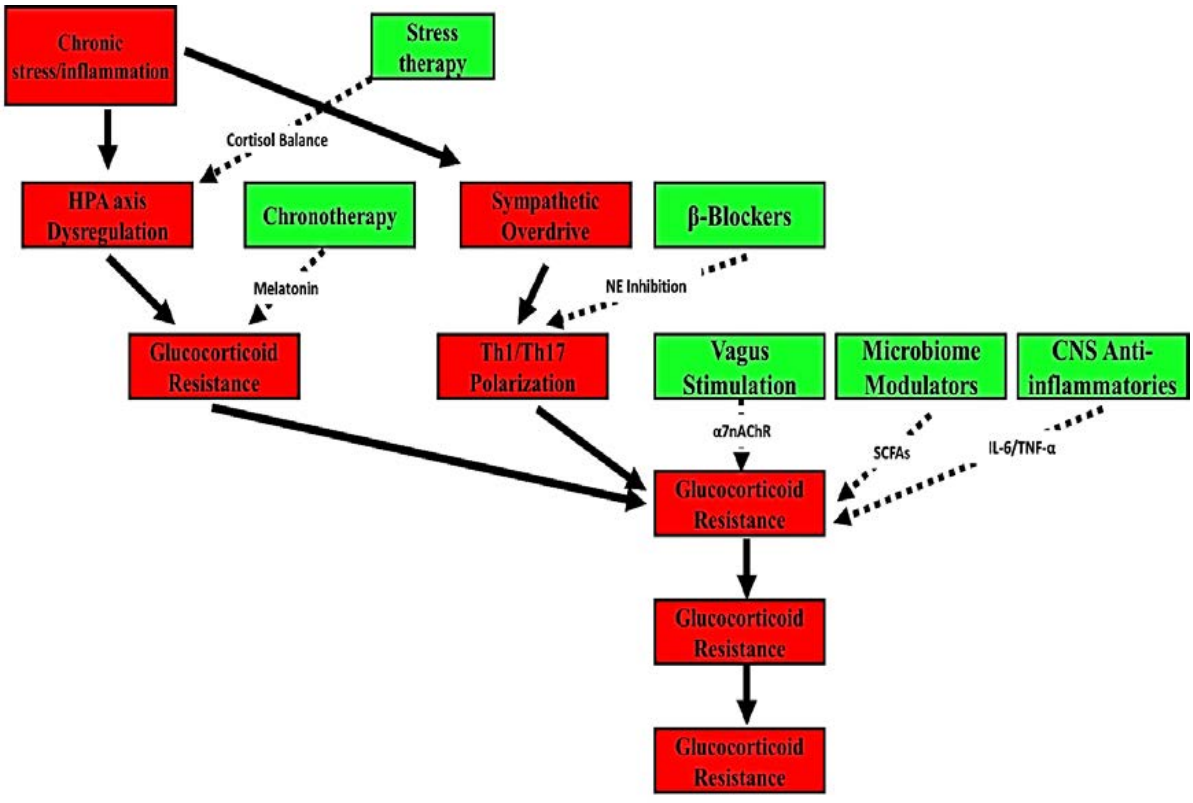

Figure 1: Neuroimmune Pathways in Autoimmune Hemolytic Anemia (AIHA) Pathogenesis. Chronic stress and inflammation trigger hypothalamic-pituitary-adrenal (HPA) axis dysregulation and sympathetic overdrive, leading to glucocorticoid resistance and Th1/Th17 polarization. These events promote autoantibody-mediated RBC destruction (red pathway). Emerging therapies (green) target key nodes: vagus stimulation (α7nAChR), β-blockers (NE inhibition), and microbiome modulators (SCFAs) to restore immune homeostasis.

5. Emerging Neuromodulatory Therapies: Targeting the Nervous System in AIHA

The neuroimmune axis presents a compelling target for therapeutic intervention in autoimmune disorders like AIHA. Traditional therapies for AIHA, including corticosteroids, immunosuppressants, and rituximab, primarily target immune cells. However, emerging strategies aim to modulate the nervous system to influence immune behavior indirectly. One such approach is vagus nerve stimulation, a technique approved for epilepsy and depression, which activates the cholinergic anti-inflammatory pathway (Bonaz et al., 2013). Vagus nerve stimulation has shown promise in preclinical autoimmune models by reducing cytokine production and promoting immune tolerance (Liu et al., 2024). Similarly, bioelectronic medicine an evolving field that employs devices to deliver targeted neural impulses offers precision in modulating immune responses via nerve pathways. Trials investigating implantable vagus nerve stimulation devices for autoimmune diseases like rheumatoid arthritis have demonstrated reductions in disease activity, suggesting a translatable potential in AIHA, particularly for steroid-refractory or relapsing cases. Pharmacologic agents targeting neuroimmune receptors such as α7nAChRs or glucocorticoid receptors also hold promise. Selective receptor modulators may fine-tune immune responses without the broad immunosuppression associated with corticosteroids. Additionally, behavioral therapies such as cognitive behavioral therapy, mindfulness, and sleep hygiene are being explored for their capacity to reduce neuroinflammatory tone and enhance immune resilience (Nemirovsky et al., 2022). Integrating neuromodulation with conventional therapies may not only improve treatment response but also minimize long-term complications. Personalized medicine approaches that consider a patient's neuroendocrine profile, stress levels, and circadian biology could guide the application of these interventions. As our understanding of neuroimmune dynamics expands, neuromodulatory therapies are poised to become a key component of comprehensive AIHA management (Table 1 & Figure 1).

Table 1: Neuroimmune Components and Therapeutic Targets in AIHA

Neuroimmune Element	Role in AIHA Pathophysiology	Key Mediators	Therapeutic Implications
HPA Axis	• Chronic stress alters cortisol • Glucocorticoid resistance	Cortisol, ACTH	• Optimize steroid use • GR modulators
Vagus Nerve	• Impaired anti-inflammatory reflex • Uncontrolled cytokines	Acetylcholine, α7nAChR	• Vagus nerve stimulation • α7nAChR agonists
Sympathetic Activity	• Enhances Th1/Th17 response • B-cell stimulation	Norepinephrine, β2-adrenergic	• β-blockers (selective) • Stress control therapy
CNS Inflammation	• Microglia release IL-1β, TNF-α • Disrupts immune balance	IL-1β, TNF-α, IL-6	• CNS-targeted anti-inflammatories
Bone Marrow Innervation	• Alters hematopoiesis • Impacts erythrocyte production	NE, SCF, CXCL12	• Neuroimmune regulation of erythropoiesis
Gut-Brain-Immune Axis	• Dysbiosis affects immune tolerance	SCFA, serotonin, vagal afferents	• Probiotic therapy • Diet modulation
Neuroendocrine Disruption	• Circadian disruption • Impairs immune checkpoints	Melatonin, cortisol rhythm	• Chronotherapy • Sleep and behavioral therapy

6. Future Perspective

As the intricate interplay between the nervous and immune systems becomes clearer, the importance of neuroimmune regulation in AIHA is emerging as a vital research avenue. While traditional treatment strategies have focused on immunosuppression, relapses and treatment resistance underscore the need for more targeted and holistic approaches. Future investigations should prioritize characterizing the neuroimmune signatures of AIHA patients, including hypothalamic-pituitary-adrenal axis responsiveness, autonomic nervous system activity, and CNS involvement through neuroimaging and biomarkers. This would allow stratification of patients based on neuroimmune dysregulation, enabling personalized medicine strategies.

Advancements in wearable technology and biosensors may soon allow real-time monitoring of circadian rhythms, stress levels, and autonomic tone in AIHA patients. These tools could help predict flares or treatment failures and guide behavioral or pharmacologic interventions. Longitudinal studies investigating how chronic stress, sleep disruption, and neuroinflammation contribute to immune dysregulation in AIHA will provide foundational data for therapeutic innovation. Ultimately, embracing neuroimmune modulation as a component of AIHA management could revolutionize treatment paradigms, reduce relapses, and improve quality of life. It also invites a broader rethinking of how autoimmunity is conceptualized not just as an immunological disorder, but as a systemic, neuroregulated condition.

7. Conclusion

AIHA is a complex disorder driven by immune dysregulation and influenced by neuroimmune interactions, including stress responses, autonomic signaling, and neuroinflammation. AIHA through a neuroimmune lens reveals new insights into relapse, treatment resistance, and disease persistence. Emerging therapies like neuromodulation and bioelectronic medicine, combined with personalized approaches, could improve outcomes. Integrating neuroimmune science into hematology offers innovative diagnostic and therapeutic strategies, advancing toward a more holistic treatment paradigm for autoimmune hematologic diseases.

Declarations

Ethics approval statement

Not applicable

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

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Author contribution

Conceptualization, Data curation, Investigation: A.K; A.A. Formal analysis, Writing, review, and editing: A.M.L. All authors have read and agreed to the published version of the manuscript

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Disclosure use of AI-assisted technologies

During the preparation of this work the authors used AI-assisted technology QuillBot, in order to check the grammar and spell in some sentences

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