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Mini Review

Neurological biomarkers in adolescent and young adult populations with hyperuricemia and gout: diagnostic potential and clinical implications

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Introduction

Hyperuricemia and gout represent significant metabolic and inflammatory disorders with increasing prevalence among adolescents and young adults (typically defined as ages 12–25 years). Epidemiological studies indicate that adolescent hyperuricemia prevalence varies significantly by geographic region and diagnostic criteria, with recent studies reporting rates ranging from 8.4% to 21.4% depending on the threshold definitions applied [1]. It is important to emphasize that research on most biomarkers in adolescent and young adult populations with hyperuricemia/gout remains in early stages, with limited prospective data available. The traditional diagnostic paradigm for hyperuricemia and gout relies primarily on serum uric acid measurements and synovial fluid monosodium urate (MSU) crystal detection [2–4]. However, these approaches have limitations: serum uric acid levels fluctuate with acute inflammatory episodes, and joint aspiration is invasive and technically demanding [2–4]. Furthermore, emerging evidence suggests that hyperuricemia exerts systemic effects beyond the musculoskeletal system, including potential impacts on neurological function through mechanisms involving oxidative stress, neuroinflammation, and blood-brain barrier (BBB) dysfunction [5]. This article critically examines the potential diagnostic utility of neurological biomarkers in adolescent and young adult populations with hyperuricemia and gout. We synthesize current evidence from 2019–2025, clarify the biological rationale linking systemic hyperuricemia to neurological biomarker alterations, and critically appraise the clinical relevance and limitations of these biomarkers for diagnostic application in this specific demographic.

Biological Rationale: Hyperuricemia and Neurological Pathophysiology

Understanding the diagnostic potential of neurological biomarkers in hyperuricemia requires appreciation of the underlying pathophysiological mechanisms. Uric acid exhibits a dual biological role: at physiological concentrations, it functions as an endogenous antioxidant accounting for up to 55% of extracellular antioxidant capacity; however, at elevated concentrations, it promotes oxidative stress, endothelial dysfunction, and inflammation [5]. The NLRP3 (NOD-like receptor family pyrin domain containing 3) inflammasome serves as a critical mechanistic link between hyperuricemia and neurological dysfunction. MSU crystals, the pathognomonic feature of gout, activate the NLRP3 inflammasome, triggering interleukin-1β (IL-1β) maturation and release [6]. The NLRP3 inflammasome is increasingly recognized as a central mediator of neuroinflammation in

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neurodegenerative diseases, with several brain-penetrant inhibitors currently in clinical development for Parkinson's disease and other central nervous system conditions [7–9]. Systemic IL-1β elevation can influence central nervous system function through multiple pathways, including vagal nerve signaling and BBB permeabilization [10]. Hyperuricemia-induced oxidative stress can compromise BBB integrity, potentially allowing peripheral inflammatory mediators to access the central nervous system and trigger astrocyte activation and neuronal injury detectable through specific biomarkers [5, 11].

Neurological Biomarkers: Diagnostic Relevance and Clinical Evidence

Neuronal injury biomarkers

Neuron-specific enolase (NSE)

Neuron-specific enolase (NSE) is a cytoplasmic enzyme specific to mature neurons, widely used for neurological injury assessment. Normal adult serum reference values are typically <16.3 ng/mL [12]. Systemic inflammation may elevate NSE levels; however, direct evidence regarding NSE alterations in gout patients is limited. Hemolysis and neuroendocrine tumors can cause false-positive results [13].

Diagnostic relevance to hyperuricemia/gout: While biological plausibility exists for NSE elevation through uric acid-induced oxidative stress, direct evidence linking NSE to hyperuricemia in adolescents remains limited. NSE lacks specificity for hyperuricemia-related neurological changes, as hemolysis and neuroendocrine tumors can cause false-positive results [13]. Currently, NSE does not demonstrate sufficient diagnostic specificity for hyperuricemia or gout in clinical practice.

Ubiquitin C-terminal Hydrolase L1 (UCH-L1)

Ubiquitin C-terminal hydrolase L1 (UCH-L1) is rapidly released following acute brain injury. The U.S. Food and Drug Administration (FDA) approved its use in combination with glial fibrillary acidic protein (GFAP) for mild traumatic brain injury diagnosis in 2018 [14]. Recent 2024 data from the BRAINI multicenter European study validated automated blood testing for GFAP and UCH-L1 to predict intracranial lesions in mild traumatic brain injury patients [15]. A 2024 JAMA Network Open study demonstrated that UCH-L1 elevates rapidly within 30–60 minutes post-trauma, with AUCs of 0.75 (30 min) and 0.73 (60 min) for diagnosing intracranial lesions; however, GFAP demonstrated superior performance (AUC 0.88–0.89) [16].

Diagnostic relevance to hyperuricemia/gout: The rapid kinetics of UCH-L1 release make it theoretically attractive for detecting acute neurological changes secondary to hyperuricemic crises. However, research specifically examining UCH-L1 in hyperuricemia or gout populations remains absent. The biomarker's primary utility appears confined to acute traumatic injury rather than metabolic or inflammatory neurological sequelae.

Axonal integrity biomarkers

Neurofilament light chain (NfL)

Serum NfL is a sensitive biomarker of axonal injury, utilized in various neurodegenerative diseases. Studies indicate that NfL levels vary significantly by age, with higher levels in younger children and gradual decline through adolescence [17]. However, direct research data on the relationship between adolescent hyperuricemia and NfL remains limited.

Diagnostic relevance to hyperuricemia/gout: The potential diagnostic utility of NfL in hyperuricemia stems from the hypothesis that chronic systemic inflammation and oxidative stress may produce subclinical axonal injury. A 2019 study found associations between elevated inflammatory markers and cognitive decline, though not specifically examining NfL in metabolic syndrome [18]. However, direct research data on the relationship between adolescent hyperuricemia and NfL remains limited. The high cost of NfL testing (typically hundreds to thousands of dollars) further limits its feasibility for routine screening in this demographic

Plasma tau proteins

Plasma phosphorylated tau at threonine 217 (p-Tau217) and threonine 181 (p-Tau181) have emerged as biomarkers for neurodegenerative diseases [19]. Recent 2024–2025 studies in heterogeneous community-based cohorts demonstrated that plasma p-Tau217 accurately classified amyloid PET-positive individuals with AUCs of 94–97%, using a cut point ≥0.338 pg/mL, and outperformed p-Tau181 [20, 21].

Diagnostic relevance to hyperuricemia/gout: The inclusion of tau proteins in hyperuricemia biomarker panels requires careful justification. While systemic inflammation may theoretically influence tau protein metabolism through microglial activation and neuroinflammatory pathways [22]. No direct evidence links plasma tau elevation to hyperuricemia or gout. The clinical significance of tau biomarkers in non-neurodegenerative populations remains unclear, and their diagnostic utility for hyperuricemia-related neurological changes is currently unsupported by empirical data. We emphasize that tau biomarkers should not be routinely applied in hyperuricemia or gout diagnostics outside research contexts.

Astrocyte and blood-brain barrier biomarkers

Glial fibrillary acidic protein (GFAP)

GFAP is an intermediate filament protein expressed in astrocytes, serving as a marker of astrocyte activation and BBB injury. In 2022, the FDA approved GFAP in combination with UCH-L1 for acute brain injury diagnosis [14]. A 2025 study using the Lumipulse platform established adult reference intervals of 10.4–92.0 ng/L, with significant age and sex differences observed [23]. Recent 2024 data demonstrated that GFAP measured within 30 minutes of traumatic brain injury had 98.1% sensitivity (95% CI 94.9–99.4%) and 34.4% specificity for CT lesions, with AUCs of 0.88 (30 min) and 0.89 (60 min) [16]. A 2022 review demonstrated that systemic inflammation may cause mild GFAP elevation, though significant elevation typically indicates central nervous system pathology [24]. Its role in adolescent gout has not been established.

Diagnostic relevance to hyperuricemia/gout: Among neurological biomarkers, GFAP holds particular theoretical relevance for hyperuricemia due to the established association between systemic inflammation, oxidative stress, and BBB dysfunction. Hyperuricemia-induced endothelial dysfunction may compromise BBB integrity, potentially triggering astrocyte activation detectable through GFAP elevation. However, as explicitly acknowledged in current literature, "its role in adolescent gout has not been established" [24]. The diagnostic potential of GFAP in hyperuricemia remains hypothetical: while systemic inflammation (characteristic of acute gout flares) may produce mild GFAP elevation, this lacks specificity for gout diagnosis and could reflect various inflammatory conditions. Furthermore, the influence of age-specific reference ranges on GFAP interpretation in adolescent populations requires formal validation. Currently, GFAP cannot be recommended as a diagnostic biomarker for hyperuricemia or gout outside research settings.

S100 calcium-binding protein B (S100β)

S100β has a short half-life (approximately 25 minutes) and can reflect acute BBB permeability changes. Normal reference values are <0.10–0.15 μg/L.25 S100β is influenced by multiple factors, including peripheral tissue injury, vigorous exercise, and body mass index (BMI), with relatively low specificity for isolated brain injury [13, 25].

Diagnostic relevance to hyperuricemia/gout: S100β is influenced by multiple confounding factors, including peripheral tissue injury, vigorous exercise, and BMI, with relatively low specificity for isolated brain injury [13,25]. In adolescent and young adult populations, physical activity patterns (including sports participation and exercise routines common among students) may significantly influence S100β levels independent of neurological pathology. This limitation substantially reduces S100β's diagnostic utility for hyperuricemia-related neurological changes in this demographic.

Inflammatory biomarkers

Interleukin-1 beta (IL-1β) and NLRP3 inflammasome

IL-1β plays a central role in gout pathogenesis. A 2020 study confirmed that urate crystals induce IL-1β maturation and release through NLRP3 inflammasome activation [6]. The NLRP3 inflammasome is increasingly recognized as a critical mediator of neuroinflammation in neurodegenerative diseases, with several brain-penetrant inhibitors currently in clinical development for Parkinson's disease and other central nervous system conditions [7–9].

Diagnostic relevance to hyperuricemia/gout: IL-1β represents the most biologically plausible neurological biomarker for hyperuricemia and gout, given its direct mechanistic link to MSU crystal-induced inflammation. Systemic IL-1β elevation during acute gout flares may affect neurological function through vagal nerve pathways and BBB modulation.10 However, clinical evidence linking peripheral IL-1β levels to specific diagnostic outcomes in gout patients remains inconsistent, and the biomarker lacks specificity for neurological versus systemic inflammatory activity. For diagnostic application, IL-1β measurement faces practical challenges: serum IL-1β levels are highly variable, influenced by circadian rhythms, acute phase responses, and sample handling procedures. While IL-1β is central to gout pathophysiology, its utility as a specific diagnostic biomarker for hyperuricemia-related neurological involvement remains unproven and requires further validation.

Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)

These pro-inflammatory cytokines are significantly elevated during acute gout attacks and chronic hyperuricemia-associated inflammation. Epidemiological studies indicate that elevated IL-6 and TNF-α are associated with neurological dysfunction in various metabolic and inflammatory conditions [26]. However, specific quantitative data in adolescent gout populations remain limited.

Diagnostic relevance to hyperuricemia/gout: The pathophysiological mechanisms likely involve chronic low-grade inflammation, endothelial dysfunction, and subsequent cerebrovascular impairment [26]. However, like IL-1β, these cytokines lack specificity for neurological pathology and primarily reflect systemic inflammatory status. Their diagnostic utility for detecting hyperuricemia-specific neurological changes is currently unsupported by direct evidence.

Metabolism-related biomarkers

The dual role of blood uric acid

Uric acid exhibits concentration-dependent biological effects: as an endogenous antioxidant, it may exert neuroprotective properties, particularly at moderate elevations. A 2025 comprehensive review summarized evidence supporting neuroprotective effects in Parkinson's and Alzheimer's disease through suppression of neuroinflammation and oxidative stress [5]. However, the review emphasized that therapeutic uric acid elevation exhibits unstable antioxidant properties, substantial individual variability, and potential adverse effects, limiting clinical applications.

Diagnostic considerations: Observational studies examining the relationship between uric acid and neurological function have yielded mixed results, with some analyses suggesting that associations may reflect confounding by metabolic comorbidities (obesity, hypertension, diabetes) rather than direct causal effects. For diagnostic purposes, serum uric acid remains the primary biochemical marker for hyperuricemia, though its fluctuation during acute inflammatory episodes necessitates careful clinical interpretation.

MicroRNA (miRNA)

Circulating miRNAs have gained attention as potential disease biomarkers due to their stability in biofluids and tissue-specific expression patterns. A 2019 review discussed miRNA biology, biogenesis mechanisms, and potential therapeutic applications across various disease contexts [27]. However, specific evidence in gout or hyperuricemia populations remains substantially limited.

Diagnostic relevance to hyperuricemia/gout: Specific miRNA signatures associated with hyperuricemia-induced inflammation or neurological sequelae have not been established. Standardization of detection methodologies and large-scale clinical validation remain significant challenges for miRNA biomarker implementation in routine diagnostic practice.

Special Considerations for Adolescent and Young Adult Populations

The designation "adolescents and young adults" (ages 12–25 years) encompasses distinct developmental stages with unique physiological and environmental characteristics relevant to biomarker interpretation. Unlike the ambiguous term "students," this demographic definition aligns with established WHO and epidemiological classifications [1].

Age-specific physiological factors

Neurological biomarkers demonstrate significant age-dependent variability. Reference ranges require age-stratification, with particular attention to pubertal status and developmental stage [17,23]. Current adult reference intervals may not apply to adolescent populations, potentially leading to misinterpretation of biomarker levels.

Lifestyle and environmental factors

Adolescents and young adults frequently experience unique stressors that may influence both hyperuricemia risk and biomarker profiles: academic pressure, sleep deprivation, irregular dietary patterns, and sedentary behaviors. These factors may exacerbate systemic inflammation and oxidative stress, potentially amplifying biomarker signals. However, the specific interactions between these lifestyle factors and neurological biomarkers in hyperuricemic populations remain unexplored in current literature.

Clinical presentation differences

Adolescent hyperuricemia often presents with atypical features compared with adult-onset disease, including higher prevalence in males, stronger associations with obesity, and potential differences in inflammatory response patterns [1]. These characteristics may influence biomarker expression and diagnostic thresholds.

Current Limitations and Critical Appraisal

Insufficient age-specific evidence

Most neurological biomarkers lack adequate validation in adolescent and young adult hyperuricemia/gout populations. Existing evidence primarily derives from adult studies or other disease contexts (traumatic brain injury, neurodegenerative diseases), limiting direct applicability to this demographic [24]. It is important to emphasize that research on most biomarkers in adolescent and young adult populations with hyperuricemia/gout remains in early stages, with limited prospective data available.

Standardization deficiencies

Detection methods, reference ranges, and sampling protocols remain unstandardized across laboratories, limiting comparability and clinical implementation. Recent studies emphasize the need for age- and sex-specific reference intervals, particularly for GFAP and NfL [17,23].

Cost-effectiveness constraints

Most neurological biomarker assays are expensive (NfL and Tau testing can cost hundreds to thousands of dollars), making them unsuitable for routine screening in adolescent populations where healthcare resource allocation prioritizes established interventions.

Specificity limitations

Current biomarkers lack specificity for hyperuricemia-induced neurological changes versus other causes of neuronal injury, inflammation, or BBB dysfunction. This limits their diagnostic utility for distinguishing hyperuricemia-related neurological sequelae from alternative etiologies.

Causality versus association

Available evidence primarily consists of observational studies that cannot establish causal relationships between hyperuricemia and neurological biomarker alterations. Mendelian randomization studies suggest some associations may reflect confounding factors rather than direct causal effects.

Future Research Directions and Clinical Implications

Prospective cohort studies

Establishment of long-term follow-up cohorts of adolescents with hyperuricemia is essential to clarify biomarker trajectories, temporal relationships with disease progression, and associations with cognitive/behavioral outcomes. Such studies should incorporate age-appropriate neurological and neuropsychological assessments.

Reference range establishment

Development of validated age- and sex-specific reference ranges for adolescents and young adults, considering developmental stages, pubertal status, and ethnic variations. This is particularly critical for GFAP and NfL, which demonstrate substantial age-related variability [17,23].

Multi-biomarker diagnostic panels

Exploration of combined biomarker testing to improve diagnostic sensitivity and specificity for hyperuricemia-related neurological involvement. The 2024 BRAINI study validated automated GFAP/UCH-L1 testing for traumatic brain injury [15], suggesting that similar approaches could be adapted for metabolic and inflammatory conditions.

Intervention studies

Evaluation of urate-lowering therapy and lifestyle interventions (dietary modification, weight management, stress reduction) effects

on neurological biomarkers, validating their utility as therapeutic monitoring tools and surrogate endpoints for neurological protection.

Mechanistic research

Elucidation of specific mechanisms by which hyperuricemia affects the nervous system through animal models and *in vitro* experiments, particularly focusing on NLRP3 inflammasome pathways, BBB integrity, and neuronal oxidative stress responses [5,11].

Integration with lifestyle factors

Investigation of how academic stress, sleep patterns, dietary habits, and physical activity common in adolescent and young adult populations interact with hyperuricemia to influence neurological biomarker profiles and clinical outcomes.

Conclusion

While various neurological biomarkers demonstrate established utility in adult neurological diseases, their application in adolescent and young adult hyperuricemia/gout populations remains exploratory and unsupported by sufficient empirical evidence. The biological rationale linking systemic hyperuricemia to neurological biomarker alterations is mechanistically coherent—spanning NLRP3 inflammasome activation, IL-1β-mediated neuroinflammation, oxidative stress pathways, and BBB dysfunction—yet the clinical translation of these mechanisms into validated diagnostic tools remains nascent. Recent 2024–2025 data demonstrate clinical validity of GFAP/UCH-L1 testing in traumatic brain injury and provide refined reference ranges for GFAP in adult populations [15,16,23], but direct applicability to hyperuricemia diagnostics is unproven, and the biomarker landscape requires substantial further development before it can inform routine practice in this demographic. Among the biomarkers examined, GFAP holds the strongest theoretical relevance to hyperuricemia-associated neurological changes by virtue of its sensitivity to BBB disruption and astrocyte activation, both plausible sequelae of uric acid-induced endothelial dysfunction. IL-1β and the NLRP3 inflammasome pathway retain the most direct mechanistic connection to gout pathophysiology; however, their lack of neurological specificity and the practical difficulties of reliable measurement constrain their diagnostic applicability. NfL offers sensitive detection of subclinical axonal injury but suffers from prohibitive cost, pronounced age-dependent variability, and the complete absence of calibration data in adolescent hyperuricemia cohorts. Tau proteins, NSE, UCH-L1, S100β, and circulating miRNAs each face analogous combinations of specificity deficits, unstandardized reference ranges, and an absence of disease-specific validation that collectively preclude clinical adoption outside research contexts. Current evidence remains insufficient to support routine clinical implementation of neurological biomarkers for hyperuricemia or gout diagnosis in adolescents and young adults. Clinical decision-making should continue to prioritize symptoms, physical examination findings, and conventional laboratory parameters—serum uric acid, acute-phase inflammatory markers, and renal function indices. The evolving recognition that hyperuricemia exerts systemic effects extending beyond the musculoskeletal system [5], combined with the increasing prevalence of hyperuricemia in adolescent and young adult populations across diverse ethnic and geographic settings [1], nonetheless establishes a compelling rationale for dedicated biomarker research in this cohort.

For adolescent and young adult populations, including university students, prioritizing modifiable risk factors—structured lifestyle modifications, academic stress management, sleep hygiene optimization, dietary purine restriction, and evidence-based urate-lowering pharmacotherapy where indicated—offers greater immediate practical value than pursuing unvalidated novel biomarker strategies. Future research must address several critical deficiencies: the establishment of age- and sex-stratified reference intervals for GFAP, NfL, and related biomarkers in healthy and hyperuricemic adolescent cohorts; the conduct of prospective longitudinal studies with embedded neuropsychological assessments to characterize biomarker trajectories relative to disease course; the design of intervention studies evaluating urate-lowering therapy effects on neurological biomarker profiles as surrogate endpoints for neurological protection; and the mechanistic elucidation of NLRP3-dependent and NLRP3-independent pathways through which sustained hyperuricemia may compromise central nervous system integrity in young individuals [7,9]. Multi-biomarker panel approaches, analogous to the validated GFAP/UCH-L1 paradigm in traumatic brain injury [15], merit adaptation and evaluation in metabolic-inflammatory disease contexts. High-quality, large-sample, multicenter longitudinal studies incorporating these methodological standards are essential to determine whether neurological biomarkers can ultimately serve a meaningful role in the early identification, risk stratification, and therapeutic monitoring of hyperuricemia and gout in adolescent and young adult populations—and, if so, to define the precise clinical contexts in which their application would be both diagnostically informative and economically justified.

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