



Review

Uhthoff's Phenomenon—A Scare or Real Threat to Multiple Sclerosis Patients? A Narrative Review

Jarosław Wojciech Szczygiał^{1,2,3,†} and Józef Alfons Opara^{1,*,†} 

¹ Institute of Physiotherapy and Health Sciences, Jerzy Kukuczka Academy of Physical Education, Ul. Mikołowska 72b, 40-065 Katowice, Poland; jwszczygial@gmail.com

² Department of Neurology, Clinical Hospital No. 1 Named After Prof. Stanisław Szyszko, Silesian University of Medicine in Katowice, Ul. 3 Maja 13/15, 41-800 Zabrze, Poland

³ Institute of Psychology, Humanitas University, Ul. Kilińskiego 43, 41-200 Sosnowiec, Poland

* Correspondence: jozef.opara70@gmail.com

† These authors contributed equally to this work.

Abstract

Uhthoff's phenomenon (UP) is a transient, fully reversible exacerbation of pre-existing neurological deficits in multiple sclerosis (MS) patients, triggered by minor elevations in core body temperature. In clinical practice, UP is a frequent source of distress, often misidentified as an acute inflammatory disease relapse. This narrative review provides a critical analysis of UP, addressing methodological heterogeneity in its epidemiological estimates, its clinical presentation, and its differential diagnosis from true relapses. Mechanistically, we synthesize traditional concepts of temperature-dependent conduction block with modern insights into neuroenergetic failure, mitochondrial dysfunction, inflammatory mediators, and autonomic dysregulation. Furthermore, this work delineates current management strategies, establishing a clear distinction between robust evidence-based interventions and expert-informed practical guidance for patient education, physical rehabilitation planning, targeted active/passive cooling, and pharmacological approaches. Characterized as a pseudo-relapse, UP occurs independently of novel focal neuroinflammation. In conclusion, an isolated episode of Uhthoff's phenomenon (UP) represents a transient, functional conduction block and does not inflict acute, permanent structural damage to the axon. However, emerging frameworks suggest that frequent, repeated episodes subject the already demyelinated axon to recurrent metabolic strain. Over time, these successive neuroenergetic crises do not directly destroy the fiber, but they may gradually exhaust the cell's metabolic reserve. This cumulative stress potentially increases long-term secondary axonal vulnerability, making the axon more susceptible to the progressive neurodegenerative processes inherent to multiple sclerosis.

Keywords: multiple sclerosis; Uhthoff's phenomenon; heat sensitivity; pseudo-relapse; temperature regulation; axonal conduction



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1. Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated neurodegenerative disorder of the central nervous system (CNS) characterized by a highly heterogeneous clinical presentation and an unpredictable disease course that frequently leads to progressive disability. While classic clinical progression is traditionally defined by acute inflammatory relapses followed by periods of remission, transient symptom fluctuations independent of novel focal neuroinflammation present an equally critical challenge in routine clinical

practice [1]. Among these, heat sensitivity stands out as one of the most prevalent and disruptive features of the disease, frequently manifesting as Uhthoff's phenomenon (UP)—a temporary, temperature-dependent worsening of pre-existing neurological deficits [1].

Recent epidemiological evidence highlights a significant escalation in the global burden of MS over the past three decades. The distribution of MS correlates strongly with geographical latitude, age of onset, and socio-demographic factors, reflecting a complex, multifactorial interplay between polygenic susceptibility and environmental triggers, such as Epstein–Barr virus (EBV) exposure and vitamin D deficiency. Analysis of the Global Burden of Disease (GBD) Study 2021 indicates that approximately 1.89 million individuals are living with MS worldwide, with over 62,000 incident cases recorded in 2021 alone [1]. This corresponds to a global prevalence rate of 23.9 cases per 100,000 population. Notably, the epidemiological burden exhibits substantial gender and age-specific asymmetry; women are approximately twice as likely as men to be diagnosed with MS, with the highest incidence rates concentrated within the young adult population aged 15 to 40 years [1]. Explicitly highlighting this gender asymmetry, the global prevalence of MS among women is estimated at 32.3 per 100,000 individuals, nearly doubling the prevalence of 15.6 per 100,000 observed in men [1]. The peak incidence of the disease occurs between 30 and 34 years of age. Consequently, the predilection of MS for young women during their peak reproductive and socio-professional years inflicts profound socio-economic burdens, severely impacting workforce participation and family planning [1].

The historical foundation of heat sensitivity in MS traces back to Wilhelm Uhthoff, a prominent German ophthalmologist who significantly shaped early neuro-ophthalmology. In 1890, Uhthoff documented a distinct clinical phenomenon involving transient visual disturbances in MS patients following physical exertion [2–4]. In his initial cohort, he observed that four out of 100 individuals experienced a “marked deterioration in visual acuity during physical effort and exhaustion,” driven by elevated core body temperature [2–4]. By 1904, Uhthoff further postulated that this reversible amblyopia was fundamentally linked to structural demyelination, particularly within the optic nerve pathways [5]. This transient exacerbation was subsequently formalized in 1961 by G. Rinklefs, who coined the term “Uhthoff's phenomenon” (UP) [6]. Over the ensuing decades, UP has expanded from its initial neuro-ophthalmological definition to encompass a broader spectrum of temperature-dependent neurological fluctuations, prompting extensive research into its precise pathophysiological mechanisms.

Historically, Davis et al. (2010) estimated that UP affects between 60% and 80% of individuals diagnosed with MS at least once during their lifetime [7]. However, as discussed comprehensively in Section 4, these widely cited prevalence ranges must be interpreted with caution due to substantial methodological heterogeneity, a heavy reliance on self-reported patient questionnaires, and the absence of standardized clinical definitions across different epidemiological cohorts [7]. Despite these statistical variations, there is a strong consensus that even minor elevations in core body temperature serve as the primary catalyst for UP [7]. While historically confined to visual acuity deficits, contemporary clinical observations indicate that thermal stress frequently exacerbates symptoms across multiple neurological domains, including postural stability, motor strength, cognitive processing, and somatosensory functions [8]. During the latter half of the 20th century, this high thermal sensitivity was leveraged diagnostically via the “hot bath test” [9,10]. This provocative tool was subsequently discontinued and fell out of clinical favor due to its low diagnostic specificity, the advent of advanced neuroimaging techniques, and the ethical implications of inducing severe, albeit temporary, neurological distress in vulnerable patients [10].

2. Methodology

2.1. Objectives

This narrative review provides a comprehensive synthesis of the historical and contemporary literature regarding Uhthoff's phenomenon (UP) in multiple sclerosis (MS). The specific objectives are as follows:

1. Formulate a precise definition of UP and contextualize its relationship with systemic thermal sensitivity in MS [7];
2. Critically appraise its epidemiology, exploring the methodological limitations and heterogeneity of current prevalence estimates [11];
3. Delineate the multifaceted pathophysiological mechanisms of UP, integrating traditional neurophysiological models with modern concepts of mitochondrial dysfunction, neuroenergetic failure, inflammatory mediators, and autonomic dysregulation;
4. Outline pragmatic clinical criteria to differentiate temperature-dependent pseudo-relapses [8] from acute inflammatory relapses;
5. Review current therapeutic and preventive management strategies, establishing a clear distinction between robust evidence-based interventions and expert-informed practical guidance regarding cooling modalities, rehabilitative planning, and pharmacological approaches.

2.2. Literature Search Strategy and Limitations

A comprehensive literature search was conducted across major electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, CINAHL, and PsycINFO. The search architecture incorporated combinations of Medical Subject Headings (MeSH) and free-text keywords related to the core focus of this review, specifically "Uhthoff's phenomenon," "multiple sclerosis," "exercise," "heat sensitivity," "rehabilitation," "cooling," "pseudo-relapse," "demyelination," and "fatigue". The comprehensive bibliographical search spanned literature published from historical inception in 1890 through April 2026.

Eligibility for inclusion comprised peer-reviewed primary studies, reviews, theses, and clinical case reports published in English or German, evaluating adult populations (≥ 18 years) with a confirmed diagnosis of MS. Eligible literature was required to investigate the clinical manifestations of Uhthoff's phenomenon, heat exposure dynamics, neurophysiological nerve conduction alterations, or the physiological impacts of exercise and physical rehabilitation. Conversely, exclusion criteria were applied to non-peer-reviewed literature, conference abstracts, gray literature, and studies focusing exclusively on pediatric MS cohorts or caregiver perspectives.

Literature screening and subsequent data extraction were conducted independently by two reviewers through an initial title and abstract analysis, followed by a rigorous full-text eligibility assessment. Discrepancies regarding study inclusion were resolved via investigator consensus. Extracted data points of interest encompassed study design, cohort characteristics, clinical phenotypes, and specific outcome measurement tools. Following this selection protocol, a total of 69 articles, foundational theses, and book chapters were identified as meeting the baseline criteria. A significant proportion of the retrieved earlier literature was classified as holding predominantly historical significance, serving to contextualize the evolution of contemporary clinical perspectives on thermal dysregulation in MS.

A key methodological limitation of this narrative review is the absence of a formal quality assessment and a structured risk-of-bias evaluation for the included studies. Unlike a systematic review, this paper did not utilize rigid scoring tools to appraise primary literature. Consequently, the synthesized findings rely on studies with highly diverse methodologies spanning different clinical eras. This approach was deliberately chosen

to allow a broad, historical integration of over a century of research—ranging from early clinical reports to microphysiological ion channel data. Nevertheless, clinicians should interpret the resulting recommendations as a qualitative expert synthesis rather than a statistically standardized analysis.

3. Definition of Uhthoff's Phenomenon

Uhthoff's phenomenon (UP) is classically defined as a transient, fully reversible exacerbation of pre-existing neurological deficits secondary to minor elevations in core body temperature, often by as little as 0.2 °C to 0.5 °C. These recrudescence symptoms characteristically resolve spontaneously once normothermia is restored. While clinical consensus and narrative reports emphasize the paroxysmal nature of these episodes—typically lasting from several minutes to a few hours—formal quantitative evidence defining their precise temporal boundaries remains limited; nevertheless, by current operational definitions, an episode must not exceed a 24 h threshold. This thermal sensitivity can be precipitated by a broad spectrum of pyrogenic and non-pyrogenic factors. These include environmental hyperthermia (e.g., hot weather, hot water immersion, and sauna use), metabolic heat production via physical exertion, psychological stress, and underlying infectious processes. Additionally, while clinical experience and limited, small-scale observational data suggest that cyclical hormonal fluctuations—such as those occurring during menstruation or ovulation—might lower the thermal threshold for symptom manifestation, this remains an emerging hypothesis that requires formal empirical validation due to the lack of robust, large-scale studies.

In contemporary neuroimmunological practice, UP is categorized as a pseudo-relapse, representing a functional clinical fluctuation driven by external or systemic stressors in the absolute absence of novel focal neuroinflammatory activity or acute demyelination within the central nervous system (CNS) [8]. Conversely, a true multiple sclerosis (MS) relapse is pathogenetically underpinned by acute, active inflammatory lesion formation, operationally defined as the onset of novel neurological symptoms or the objective worsening of stable deficits persisting for a minimum of 24 to 48 h, occurring in a state of clinical stability and independent of confounding systemic triggers [9,10]. Differentiating these entities is of paramount clinical importance; pyrexia, for instance, serves a dual role as both an immediate physical trigger for UP and a critical diagnostic indicator of an underlying pathological process—such as a urinary tract infection—that requires prompt targeted antimicrobial intervention rather than inappropriate corticosteroid immunotherapy.

4. The Epidemiology and Clinical Significance of Heat Sensitivity

Systemic heat sensitivity represents one of the most prevalent yet clinically underestimated facets of multiple sclerosis (MS). Welfare reports and aggregated literature frequently estimate that Uhthoff's phenomenon (UP), or broader thermal sensitivity, affects approximately 60% to 80% of individuals with MS [7]. However, these figures exhibit substantial variability. This statistical fluctuation is primarily driven by striking methodological heterogeneity, including divergent operational definitions of heat sensitivity, a heavy reliance on subjective patient recall versus objective neurophysiological testing, and regional variations in climatic exposure among the populations studied [11]. Illustrating this variability, specific longitudinal observations report a lower baseline of 52% of patients experiencing manifest UP over follow-up periods spanning one to twenty years. Crucially, because the majority of historical prevalence data relies heavily on self-reported questionnaires, they remain highly vulnerable to recall bias, representing a lower tier in the hierarchy of clinical evidence compared to standardized physiological challenge protocols. Furthermore, the clinical expression of thermal stress is highly widespread; among MS patients exhibiting

UP, up to 88% report concomitant non-visual neurological exacerbations, compared to only 30% of heat-sensitive individuals without classical visual amblyopia [11].

Regarding temporal dynamics, while a minority of patients (approximately 16%) demonstrate complete clinical resolution of persistent thermal vulnerability within an eight-week window, prolonged symptom susceptibility beyond two months correlates heavily with compromised remyelination and chronic axonal vulnerability. For most individuals, the clinical presentation of UP is highly stereotyped and predictable, manifesting as “patterned” symptom exacerbations unique to the patient [11]. While this clinical predictability can empower patients to recognize pseudo-relapses independently, it frequently engenders hyper-vigilance, leading to maladaptive behaviors such as the systematic avoidance of physical, rehabilitative, and social activities [11].

Early hypotheses regarding the etiology of MS-related thermal sensitivity, such as those postulated by Guthrie and Nelson, suggested a highly multifactorial framework encompassing transient serum calcium fluctuations, primitive models of ion channel blockade, altered peripheral circulation, and heat shock protein expression [12]. However, contemporary neurobiological insights have heavily refined this paradigm. Modern concepts indicate that while these systemic circulatory and humoral shifts play a minor contributory role, the primary drivers of thermal vulnerability are structurally anchored within the demyelinated axon itself. Specifically, as detailed in Section 5, the pathomechanism is now understood to involve an intricate interplay between temperature-dependent conduction blocks, acute neuroenergetic failure, mitochondrial dysfunction, and focal autonomic dysregulation, which collectively lower the physiological threshold required to disrupt compromised neurological pathways.

Importantly, current literature exhibits profound gaps regarding the lifespan presentation of UP, as pediatric MS cohorts are systematically excluded from thermal tolerance trials. This exclusion leaves a significant gap in understanding how heat sensitivity affects younger patients during early neurodevelopment. Furthermore, the current literature contains virtually no data exploring how UP manifestations vary across diverse ethnic groups or distinct geographical populations. Consequently, any potential epidemiological variations remain entirely speculative, representing an unverified concept and a critical blind spot in global neuroimmunological care that warrants systematic future research.

Šilarová et al. performed a scoping review of literature on definition, prevalence, etiology, and management of exercise-induced heat sensitivity (EIHS) in patients with MS. Proposing the definition of EIHS, the authors have indicated that elements pertaining to environmental intolerance are reported in 29–80% of all people living with MS [13]. The mechanisms underlying EIHS are not yet fully elucidated but appear to include axon demyelination, central nervous system lesions, abnormal sudomotor function and sweating, abnormal afferent thermosensory function, disease stability, and abnormal neuropsychological responses [13]. The severity of EIHS is contingent upon the applied exercise modality, intensity, and format, with the potential for further reduction through the implementation of various cooling interventions or garments prior to and/or during exercise [13].

5. Pathophysiological Mechanisms of Uhthoff’s Phenomenon

Many researchers have tried to explain the sensitivity to heat and heat reactions in MS [14,15]. Efforts to understand Uhthoff’s phenomenon (UP) now span over a century.

Structural demyelination forces voltage-gated sodium channels to redistribute [16–19]. They upregulate along the denuded axolemma to maintain basic impulse conduction. However, this remodeling creates a high metabolic cost. The Na⁺/K⁺-ATPase pump requires significantly more ATP to stabilize resting membrane potentials. Elevated core body temperature severely disrupts this fragile energy balance. It triggers mitochondrial

dysfunction and reduces ATP synthesis [20,21]. At the same time, metabolic demand spikes sharply. Minor temperature increases also accelerate ion kinetics and alter channel gating. Specifically, heat accelerates the inactivation rate of voltage-gated sodium channels. Demyelination eliminates the axonal safety factor, leaving no functional reserve. As a result, even micro-elevations in temperature tip the vulnerable axon into a temporary conduction block.

Systemic heat sensitivity in MS is further exacerbated by autonomic dysregulation. Demyelinating lesions within central autonomic pathways frequently impair sudomotor responses and blunt peripheral thermoregulatory effector mechanisms [21]. Because the body cannot efficiently dissipate heat, a maladaptive cycle is established, thereby lowering the physiological threshold for UP manifestation even in the absolute absence of active, novel neuroinflammation [21].

Contextualizing these systemic vulnerabilities, Davis et al. categorized thermoregulatory disturbances in MS into five distinct clinical and physiological domains: (1) subjective heat sensitivity, (2) altered central regulation of core body temperature, (3) compromised responsiveness of thermoregulatory effectors, (4) heat-induced central fatigue, and (5) targeted interventions aimed at preserving neurological function during thermal stress [22].

To quantify these electrophysiological alterations, Humm et al. conducted a foundational objective assessment in a cohort of 20 MS patients, utilizing motor-evoked potentials (MEPs) to evaluate central axonal conduction kinetics under thermal duress [23]. Their findings demonstrated that even minor temperature elevations induced a significant prolongation of the central motor conduction time (CMCT, $p = 0.037$), directly capturing the real-time slowing of motor fiber conduction velocity [23]. Crucially, this subclinical electrophysiological degradation translated directly into manifest functional impairment, as evidenced by a highly significant reduction in objective walking speed ($p = 0.0002$) [23].

Beyond generalized neurological deficits, Uhthoff's phenomenon is distinctly observed in patients presenting with internuclear ophthalmoplegia (INO)—a localized brainstem syndrome resulting from structural damage to the medial longitudinal fasciculus (MLF) [24]. The MLF serves as a critical, heavily myelinated pathway interconnecting the contralateral abducens nerve nucleus with the ipsilateral oculomotor nerve motor nucleus to coordinate conjugate horizontal gaze. Clinically, INO manifests as impaired adduction of the ipsilateral eye during lateral conjugate movements, accompanied by a dissociated horizontal nystagmus of the contralateral abducting eye. These specific mechanisms seem consistent with central demyelination, widely considered pathognomonic when presenting bilaterally in young adults. Less frequent etiologies include brainstem neoplasms, syringobulbia, acute drug toxicities, and Wernicke's encephalopathy. Given its highly stereotyped anatomy and easily quantifiable deficits, Leigh et al. postulated that INO represents an ideal, reproducible in vivo model for examining the real-time neurophysiological impacts of thermal stress on axonal transmission, as well as evaluating the efficacy of novel neuroprotective interventions [24].

Utilizing this specific clinical model, Davis et al. demonstrated in a cohort of eight MS patients that an elevation in core body temperature by as little as 0.8 °C induced a measurable reduction in the velocity and tracking efficiency of adductive saccades [7]. This transient functional decay is fundamentally driven by a temperature-dependent deceleration in axonal conduction kinetics [7]. Crucially, this impairment remains fully reversible; subsequent core body cooling actively mitigates these saccadic deficits, restoring baseline oculomotor performance [7].

6. Clinical Presentation and Diagnostics

6.1. Thermal and Non-Thermal Triggers of Uhthoff's Phenomenon

Uhthoff's phenomenon (UP) is characterized by its high susceptibility to various exogenous and endogenous factors that alter core body temperature or autonomic stability. Based on current clinical observations, the primary precipitating factors contributing to these transient neurological exacerbations are classified into the following domains [8]:

1. **Elevated Environmental Temperature and Ambient Humidity:** Prolonged exposure to high seasonal ambient heat, poorly ventilated indoor environments, and the usage of excessively insulating clothing;
2. **Metabolic Heat Production via Physical Exertion:** Sustained physical effort, particularly prolonged aerobic activities or high-intensity rehabilitation;
3. **Infectious and Post-Vaccination Pyrexia:** Systemic fever secondary to underlying acute infectious processes—most notably upper respiratory tract infections and urinary tract infections (UTIs)—as well as transient febrile reactions following vaccinations;
4. **Exogenous Thermal Immersion and Radiant Heat Exposure:** Direct exposure to hot baths, showers, saunas, Jacuzzis, heated therapeutic pools, or prolonged sun exposure;
5. **Endocrine and Neuroendocrine Fluctuations:** Transient core temperature spikes and vasomotor symptoms, such as hot flashes occurring during the perimenopausal period.

While classical ambient and metabolic thermal triggers represent firmly established clinical facts supported by extensive physiological data, the precise molecular mechanisms underpinning non-thermal triggers, such as endogenous neuroendocrine fluctuations, remain an emerging concept that warrants cautious interpretation. It is hypothesized that cyclical variations in progesterone and estrogen directly alter neural membrane excitability and lower the intrinsic safety factor of demyelinated axons. However, because robust data tracking the relative prevalence and precise physiological impact of these hormonal shifts are currently lacking, this neuroendocrine link must be explicitly categorized as a compelling hypothesis rather than an established clinical fact.

6.2. Clinical Manifestations and Phenotypes of Uhthoff's Phenomenon

The clinical presentation of Uhthoff's phenomenon (UP) is highly heterogeneous, directly reflecting the anatomical topography of pre-existing, clinically silent, or chronically demyelinated lesions within the central nervous system (CNS). Under thermal stress, these subclinical deficits manifest across multiple functional domains [8,16]:

- **Neuro-Ophthalmological Symptoms:** Characterized by transient visual acuity degradation (classic Uhthoff's amblyopia), impaired contrast sensitivity, glare intolerance, chromatopsia (color desaturation), and the temporary exacerbation of pre-existing diplopia or oscillopsia secondary to nystagmus [11,14].
- **Motor and Coordinate Symptoms:** Manifesting as acute, reversible lower limb paresis, increased spasticity, foot drop, postural instability, ataxia, and a quantifiable deceleration in gait velocity [19,23].
- **Somatosensory Symptoms:** Precipitating or intensifying paroxysmal paresthesia, hypoesthesia, dysesthesia, or burning neuropathic pain [8].
- **Cognitive and Autonomic Symptoms:** Encompassing transient slowing of information processing speed, attention deficits, and acute worsening of autonomic dysregulation, such as urinary urgency, incomplete bladder emptying, and orthostatic intolerance [8].

A prominent and pervasive manifestation of thermal stress is the acute exacerbation of fatigue. While general MS-related fatigue is highly prevalent—affecting an estimated 75% to 90% of patients—its interaction with temperature is particularly profound, with literature

frequently indicating that heat exposure worsens fatigue in approximately 69% to 92% of individuals. However, these exceptionally wide ranges must be critically evaluated, as they rely almost exclusively on self-reported patient questionnaires and exhibit substantial heterogeneity based on regional climate variations.

This thermal-fatigue interplay has recently been contextualized within discussions of global climate change and escalating heatwave frequencies. However, it must be explicitly emphasized that the direct epidemiological and socio-economic impact of climate shifts on the daily presentation of UP is strictly a theoretical model with a highly limited evidence base. While this environmental trend represents a plausible emerging concern for the MS community, any proposals for public health interventions or occupational accommodations remain purely speculative until robust empirical data become available. Notably, some evidence suggests that patients with relapsing–remitting MS (RRMS) may exhibit a persistently elevated resting core body temperature, which directly correlates with baseline fatigue severity even in the absence of external thermal challenges [4].

The transient recurrence of these multi-domain symptoms carries severe secondary psychological and behavioral consequences. The predictable yet distressing nature of UP frequently induces profound kinesiophobia and a heightened fear of falling [25,26]. Epidemiological data indicate that up to 37% of individuals with MS experience a pervasive fear of falling, while actual fall prevalence reaches 50%. When amplified by thermal stress, this anxiety engenders a maladaptive cycle of hyper-vigilance. Consequently, patients often engage in the systematic avoidance of physical rehabilitation and essential social activities, inadvertently accelerating physical deconditioning and severely diminishing their overall quality of life [27,28].

6.3. Clinical Course and Prognosis

The clinical course of Uhthoff's phenomenon (UP) is typically benign, characterized by a highly favorable long-term functional prognosis. Manifestations generally initiate within minutes of exposure to thermal stress or physical exertion and resolve spontaneously upon core body cooling, cessation of activity, or cessation of the precipitating factor [29]. Conventionally, symptoms are expected to subside within a 24 h window; however, as discussed further in Section 6.5, this temporal boundary serves strictly as an empirical operational consensus rather than a definitive, biologically validated rule. Chronic or permanent neurological sequelae directly attributable to UP are exceedingly rare [29].

6.4. Diagnostic Assessment and Differential Evaluation

The clinical diagnosis of Uhthoff's phenomenon (UP) fundamentally relies on a meticulous, structured patient anamnesis. Evaluating a suspected presentation requires confirming a stereotypical, fully reversible recrudescence of pre-existing neurological deficits that is strictly linked temporally to an identifiable thermal stressor. In routine clinical practice, provocative thermal testing (such as passive heating protocols) is rarely warranted due to the transient risk of inducing falls or severe central fatigue. Instead, practitioners should rely on validated, heat-neutral functional metrics. These include low-contrast visual acuity charts; the Timed 25-Foot Walk (T25FW) for ambulatory endurance; and the Nine-Hole Peg Test (NHPT) for upper extremity fine motor coordination. Cognitive performance can be screened utilizing the Symbol Digit Modalities Test (SDMT). Structured symptom diaries that log ambient meteorological fluctuations, the intensity of physical activity, and systemic hydration status are highly valuable [29]. However, a widely adopted, validated clinical instrument specifically optimized for UP remains unavailable, highlighting an urgent call-to-action for international neuroimmunological societies [29].

6.5. Differential Diagnosis

The paramount objective in the differential evaluation of thermal sensitivity is distinguishing Uhthoff's phenomenon (UP) from a true, active multiple sclerosis (MS) relapse. As a functional pseudo-relapse, UP reflects a transient conduction failure along chronically demyelinated, vulnerable pathways under thermal duress, operating in the absolute absence of novel focal neuroinflammation [16,22]. Conversely, a true MS relapse is pathogenetically defined by acute focal inflammatory demyelinating activity and lesion formation within the central nervous system (CNS) [15]. Operationally, according to contemporary consensus criteria, a true relapse requires the emergence of novel neurological symptoms or the objective, significant escalation of stable symptoms persisting for a minimum 24 h threshold, occurring in a state of clinical stability and independent of confounding systemic stressors [30,31].

Because pyrexia and underlying infectious processes can simultaneously act as immediate physical triggers for UP and coincide temporally with an actual inflammatory relapse, a rigorous, structured diagnostic approach is essential. Clinical priority must be directed toward the prompt screening and eradication of reversible systemic causes—most notably urinary tract and respiratory infections—while systematically monitoring for red flags that denote a true relapse [8].

Table 1 presents differential diagnosis, pathophysiological mechanisms, and clinical management of Uhthoff's Phenomenon vs. true inflammatory relapse.

Table 1. Differential diagnosis, pathophysiological mechanisms, and clinical management of Uhthoff's phenomenon vs. true inflammatory relapse.

Feature	Uhthoff's Phenomenon (Pseudo-Relapse)	True Inflammatory Relapse
Pathophysiological Substrate	Temperature-dependent axonal conduction block; mitochondrial dysfunction and neuroenergetic failure; central autonomic dysregulation [7].	Acute focal autoimmune neuroinflammation; active demyelination [15]; blood–brain barrier disruption with novel lesion formation.
Deficit Pattern	Reversible recrudescence of pre-existing neurological deficits (highly stereotyped and familiar to the patient) [16].	Emergence of novel neurological symptoms or profound, objective escalation of previously stable deficits.
Precipitating Triggers	Exogenous thermal exposure (ambient heat, hot water immersion), metabolic heat (physical exertion), systemic pyrexia/infection, or dehydration.	Often idiopathic; may be modulated by chronic systemic stress, the postpartum period, or immunomodulatory therapy non-adherence.
Temporal Kinetics	Rapid onset (minutes); resolves spontaneously upon cooling/rest; typically persists < 24 h [Note 1].	Prolonged evolution (hours to days); deficits persist > 24–48 h; recovery occurs gradually over weeks to months.
Objective Examination	Typically unchanged from post-cooling clinical baseline once normothermia is fully restored.	Demonstrates novel, objective focal deficits on standardized neurological examination (e.g., EDSS score shifts).
Neuroimaging (MRI)	No novel demyelinating activity or active lesion load expected.	Frequently demonstrates novel T ₂ -hyperintense or gadolinium-enhancing lesions (not strictly mandatory for clinical diagnosis).
Immediate Action	Targeted core body cooling, physical rest, aggressive rehydration; screening/treatment for occult infections; antipyretics.	Verification and exclusion of systemic infection; initiation of high-dose corticosteroid therapy or plasma exchange if indicated.

Notes on Evidence Strength and Methodological Heterogeneity: [Note 1] Temporal Thresholds: The arbitrary 24 h boundary separating a pseudo-relapse from a true relapse represents an empirical operational consensus used in clinical practice to guide immediate triage rather than a strictly validated biological threshold established by robust randomized controlled trials. Clinicians must note that real-world presentations may overlap, creating a risk for diagnostic error if a slow-resolving pseudo-relapse or a mild true relapse occurs near this threshold.

7. Management and Prevention Strategies

Patient Education and Pragmatic Lifestyle Modifications

The foundational milestone in managing Uhthoff's phenomenon (UP) relies on structured patient education, with primary clinical emphasis placed on demystifying the transient nature of temperature-dependent functional decay. Patients must be reassured that these acute exacerbations represent fully reversible neuro-functional fluctuations rather than active focal neuroinflammation or definitive disease progression. Expert consensus frequently recommends scheduling physically demanding tasks and therapeutic exercises during the cooler early morning or late evening hours to minimize metabolic heat accumulation. Additional expert-informed practical strategies encompass maintaining aggressive systemic hydration, utilizing lightweight, highly breathable garments, seeking shaded environments, and utilizing air-conditioned spaces whenever feasible.

Physical Rehabilitation and Exercise Planning

Physical activity is crucial for patients with multiple sclerosis [32], but metabolic heat production during exercise often triggers UP, requiring customized rehabilitation planning. Continuous aerobic training should generally be replaced with interval protocols featuring short exercise bouts followed by mandatory rest periods. Progressive resistance training is also highly recommended because it induces lower metabolic heat accumulation compared to sustained cardiovascular exertion. To ensure patient safety, all training sessions must be conducted in strictly climate-controlled indoor environments where ideal room temperatures range between 18 °C and 20 °C [33,34]. Aquatic therapy represents another highly effective modality, provided that the therapeutic pool temperature remains strictly below 29 °C.

Active and Passive Cooling Modalities

Cooling strategies represent the primary physical countermeasure against UP, and these approaches are broadly divided into active and passive modalities. Active cooling involves the direct application of thermal extraction technologies, such as lightweight cooling garments, the efficacy of which is validated by several systematic reviews and small randomized controlled trials (Evidence Level II) [35–44]. By utilizing these garments, patients demonstrate a quantifiable improvement in walking capacity and a significant reduction in fatigue during thermal stress, particularly when implementing pre-cooling protocols (e.g., wearing ice vests for 30 to 60 min before physical therapy). A recent 2023 systematic review and meta-analysis by Stevens et al. conclusively demonstrated that cooling clothing significantly improves physical function, mobility, and exercise tolerance in people with MS [39]. Cold-water immersion of limbs provides rapid symptomatic relief during an acute pseudo-relapse [40]. Passive cooling relies on environmental adjustments, including the aggressive ingestion of ice slurry or cold fluids during rest intervals, head/neck cooling [44].

Pharmacological Interventions

Pharmacological management of UP is strictly reserved for patients presenting with severe, lifestyle-limiting thermal vulnerability [16]. The primary approved therapeutic option is dalfampridine (extended-release 4-aminopyridine), an agent that acts as a selective voltage-gated potassium channel blocker [45,46]. Because structural demyelination exposes the underlying axolemmal potassium channels, it causes abnormal current leakage and subsequent conduction failure; dalfampridine directly blocks these uncovered channels to prolong the action potential duration [15,22,45]. By actively enhancing the axonal safety factor, this pharmacological blockade improves signal propagation, improving objective walking speed under mild thermal duress [46]. Alternative empirical strategies focus on targeted antipyretic therapy (such as acetaminophen or ibuprofen) during infectious pyrexia to eliminate the immediate physical catalyst for pseudo-relapses.

8. Conclusions and Future Directions

Uhthoff's phenomenon remains a classic yet clinically significant manifestation of multiple sclerosis, representing a transient and fully reversible pseudo-relapse rather than active neuroinflammation [7,16]. Structurally anchored within the demyelinated axon, its underlying mechanism involves a critical interplay of neuroenergetic compromise, temperature-dependent conduction blocks, and transient mitochondrial dysfunction [16,17]. Future neuroimmunological research must address three critical pillars: the development and validation of a disease-specific patient-reported outcome (PRO) instrument to standardize emerging trials [29]; the further exploration of molecular mechanisms driving non-thermal triggers; and the adaptation of climatic education and public health strategies to protect heat-sensitive MS populations during extreme ambient heatwaves [42]. Systematic, proactive, and interdisciplinary care remains essential to preserve quality of life and maintain functional autonomy in individuals living with multiple sclerosis.

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