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## Uhthoff Phenomenon

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## Introduction

Uhthoff's phenomenon (also known as Uhthoff sign or Uhthoff syndrome) is described as temporary, short-lived (less than 24 hours) and stereotyped worsening of neurological function among multiple sclerosis patients in response to increases in core body temperature. This phenomenon is named after Wilhelm Uhthoff, a German ophthalmologist who described it. In 1890, Uhthoff first described exercise-induced amblyopia in multiple sclerosis patients. In 1961, this phenomenon was given his surname, Uhthoff's Phenomenon (UP), by G. Ricklefs[1]. In four out of 100 MS patients, Uhthoff observed the appearance of reversible optic symptoms induced by an increase in body temperature, "marked deterioration of visual acuity during physical exercise and exhausting"[2]. Subsequent observations have shown that the same physiological mechanism responsible for visual dysfunction in the setting of heat exposure, are also responsible for a variety of other neurological symptoms experienced by MS patients.

When Uhthoff studied this phenomenon, exercise was thought to be the etiology, and the significance of elevation in body temperature escaped his notice. Six decades later in 1950, the hot bath test was developed based on this phenomenon and was used as a diagnostic test for multiple sclerosis. By 1980, with advancement in neuroimaging, hot bath test began to be replaced by other diagnostic tests such as MRI and cerebrospinal fluid analysis because of its unspecific nature and potential complications. The temporary worsening of neurological function in response to heat exposure affects the physical and cognitive function of multiple sclerosis patients and interfere with their activities of daily life and functional capacity. This worsening needs to be differentiated from a true relapse or exacerbation of MS. An understanding of this phenomenon and its pathophysiology, therefore, is essential for recognition and appropriate treatment.

## Etiology

Uhthoff's phenomenon is most commonly observed in multiple sclerosis but may occur in other optic neuropathies or disorders of afferent pathways[3] for example neuromyelitis optica. In multiple sclerosis patients, several factors including the blockade of ion channels, heat shock proteins, circulatory changes, effects of serum calcium and unidentified humoral substance have been hypothesized and investigated as a cause of Uhthoff's phenomenon. Temperature sensitive conduction blockade of partially demyelinated axons in the demyelinated plaques is the most widely accepted mechanism. Several other factors including perimenstrual period, exercise, fever, sun-tanning, hot shower, sauna, psychological stress and even hot meal and smoking of cigarettes have been reported in the literature as triggers for Uhthoff's phenomenon[4].

## Epidemiology

Between 60% to 80% of patients with multiple sclerosis (MS) exhibit Uhthoff's phenomenon with heat exposure. In one study, 52% reported experiencing Uhthoff's phenomenon, with a follow-up range of 1 to 20 years. Of the MS patients with Uhthoff's phenomenon, 88% experienced non-visual heat-related phenomena compared with 30%

without Uhthoff's phenomenon. About 16% of patients experienced complete recovery in 8 weeks and persistence of the sign beyond 2 months may be a marker of poor remyelination[1][5].

## Pathophysiology

The precise mechanisms of Uhthoff's phenomenon are not completely understood but are likely due to a combination of structural and physiological changes within the demyelinated axons in the central nervous system (CNS) in the setting of the elevated core body temperature. Studies have shown a decrease in conduction velocity in response to an increase in temperature in MS patients[6]. The temperature related slowing of conduction velocity can be reversed with cooling, and this has been shown in experiments studying the adduction velocity in patients with internuclear ophthalmoplegia (INO) in MS. Adduction velocity of eye movements in MS-related INO as measured by infrared eye movement recording techniques was reduced by a systematic increase in core body temperature and reversed to baseline with active cooling[7].

The normal myelinated nerve is a highly specialized structure, with clustering of sodium channels at the nodes of Ranvier. This facilitates saltatory conduction, whereas demyelination results in widening of the nodal region leading to the transformation of faster saltatory conduction to slower membrane conduction. Segmental demyelination involves both a primary derangement in sodium channel-mediated axonal depolarization and unmasking of potassium channels resulting in K efflux and, thereby, hyperpolarization which surpasses the action potential-generating processes. Newly assembled sodium channels are subsequently inserted within the axonal membrane as an ion channel adaptation, but the newly incorporated sodium channels may exhibit altered physiological properties. Temperature escalation of as little as 0.2 C to 0.5 C is sufficient to close the axonally-derived sodium channel and terminate the depolarization phase of the action potential. Demyelination reduces the safety factor of axons, defined as the ratio of the current available to initiate an action potential to the minimal current required. Increase in temperature further reduces the axon's safety factor. Hence, an increase in temperature (even as little as 0.5 C) in individuals with Multiple sclerosis results in closure of the voltage-gated sodium channels in demyelinated axons, thereby compromising action potential depolarization and decreases the safety threshold for high-fidelity nerve transmissions[8]. This can produce abnormalities ranging from delayed conduction to complete conduction block and clinically manifests as worsened MS symptom, eg, decreased visual acuity or double vision, etc. Almost all the precipitating factors of Uhthoff phenomenon cause elevated core body temperature.

## History and Physical

Events preceding the worsening of neurological symptom should be analyzed during history taking. Factors including exercise, taking a hot bath or shower, exposure to sun, menstrual cycle, psychological stress, hot meals, fever, and infection should be addressed as any of these can precipitate worsening of the symptoms in MS patients. Transient worsening of the symptoms induced by such factors is termed 'pseudo exacerbation' or 'pseudo-relapse' as opposed to a true relapse or exacerbation in MS patients. This worsening typically should last less than 24 hours. Relapse or exacerbation is the hallmark of relapsing MS and is characterized by new focal neurological deficits lasting for at least 24 hours in the absence of fever or infection. Often, a detailed history is able to differentiate a true relapse from a pseudo-relapse. Examination reveals various neurological deficits pertaining to the location of demyelination including amblyopia, nystagmus, INO, muscular weakness, and abnormal reflexes.

## Evaluation

Episodes of Uhthoff's phenomena are generally considered to be the result of established demyelinating plaques in the setting of thermal stress. The key to making a diagnosis is detailed history from the patient regarding the circumstances in which the symptoms appeared. In patients with pseudo-relapse, care should be taken to rule out common precipitating factors like urinary tract infection, upper respiratory tract infection or metabolic abnormalities through laboratory tests.

## Treatment / Management

A fundamental principle in the prevention and treatment of Uhthoff's phenomena is to be familiar with the antecedent factors that can result in elevation of core body temperature, and their corresponding impact on the patient's neurological functioning and safety. Patients should be counseled about the stimulating effects of taking hot showers or baths regarding reducing appendicular and core muscle strength leading to profound weakness and thereby placing them in grave danger of drowning. Also, they should be cautioned against sauna, exposure to the sun when the outside temperature is greater than 30 C, hydrotherapy with water at high temperatures, short-wave radiotherapy, and paraffin application. Patients should be advised about performing an exercise during early morning and late evening hours when the temperature is cooler.

Uhthoff phenomenon fully resolves following variable periods of rest (generally ranging from minutes to an hour), and under circumstances where heat stressors are removed, or active cooling measures are applied. Simple and convenient strategies such as taking cold showers, application of ice packs, use of regional cooling devices, and cold beverages can also be tried for heat sensitivity. Cooling garments have been shown to improve neurological function (motor performance and visual acuity) and perceived subjective benefits (feeling less fatigued) in MS patients with Uhthoff's phenomenon.

There are reports showing that oral administration of 4-aminopyridine reduces the worsening of the visual impairment after an increase in body temperature in MS patients[9]. 4-Aminopyridine (4-AP) is a dose-related potassium channel blocker that prolongs action potential duration by reducing potassium efflux and thereby increasing the hyperpolarization threshold. It enhances the fidelity of conduction in segmentally demyelinated nerve fibers. FDA has approved dalfampridine, an extended release formulation of this agent in improving the walking capacity of MS patients.

## Pearls and Other Issues

Differentiation between Uhthoff's phenomena and multiple sclerosis exacerbations is of paramount importance to avoid the harm of unnecessary and additional courses of corticosteroid treatments and plasma exchange in addition to the risk of cessation of effective disease-modifying therapy, and ultimately rendering the patient vulnerable to the risks associated with escalation to a higher efficacy disease-modifying therapy, which usually are associated with higher side effect profile.

## Enhancing Healthcare Team Outcomes

The main strategy in the prevention and treatment of Uhthoff's phenomena or other pseudo relapses is to be familiar with the precipitating factors. Educating patients about the triggers and measures to avoid such triggers is important. Patients with MS usually need a multidisciplinary team that consists of the primary care provider, neurologist, and other specialists depending on the functional status, eg. ophthalmologist and urologist as well as physical and occupational therapists and social workers. Early and easy access to a care coordinator and education may decrease unnecessary emergency room visits and enhance patient outcomes.

## Questions

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