



GRIERSON-GOPALAN SYNDROME: A COMPREHENSIVE NARRATIVE REVIEW OF BURNING FEET SYNDROME

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Introduction

Imagine lying in bed at night, ready to surrender to sleep, only to be met with an unrelenting sensation that your feet are on fire. The sheets feel unbearably hot, the cool air of the room offers no relief, and no position seems to quiet the gnawing heat radiating from the soles upward. For millions of individuals worldwide, this is not a fleeting discomfort but a chronic, often misunderstood reality. This condition—clinically recognized as **Burning Feet Syndrome (BFS)** or **Grierson-Gopalan syndrome**—represents one of the most distressing yet underdiagnosed manifestations of peripheral nerve dysfunction .

The syndrome derives its eponymous name from two pioneering physicians: **Sir James Grierson**, who first documented the symptom complex in 1826, and **Dr. Gopalan**, who provided a detailed clinical description in 1946 . Despite nearly two centuries of medical recognition, Grierson-Gopalan syndrome remains shrouded in diagnostic ambiguity. It is not a disease in itself but rather a clinical phenotype—a constellation of sensory disturbances that signals an underlying pathological process ranging from metabolic derangements and toxic exposures to genetic predispositions and idiopathic small fiber neuropathy .

The global burden of this syndrome is difficult to quantify precisely, largely due to inconsistent diagnostic criteria and the tendency of clinicians to dismiss it as vague or psychosomatic . However, with the rising prevalence of diabetes mellitus, chronic alcoholism, and nutritional deficiencies worldwide, BFS is increasingly encountered across primary care, neurology, endocrinology, and podiatry clinics. This narrative review aims to illuminate the historical context, pathophysiological mechanisms, clinical presentation, diagnostic approach, and evolving therapeutic landscape of Grierson-Gopalan syndrome, offering a holistic perspective for clinicians, researchers, and patients alike.



Historical Context and Nomenclature

The earliest written account of burning feet dates back to 1826, when Grierson described patients experiencing intense burning sensations localized to the feet, often without visible dermatological changes. For over a century, the condition languished in medical obscurity, frequently attributed to hysteria or malingering. It was not until 1946 that Gopalan revisited the syndrome, characterizing it more precisely in the context of nutritional deficiency and tropical climates .

The dual eponym “Grierson-Gopalan” now honors both contributions, though the condition is more colloquially termed “burning feet syndrome” in contemporary literature. Historical reports from Asia and the Far East describe seasonal outbreaks during hot summers, suggesting environmental and dietary factors may have played a significant role in early case series .

Etiology: A Multifactorial Spectrum

Grierson-Gopalan syndrome is fundamentally a symptom complex with diverse etiological roots. Understanding these causes is essential, as treatment invariably targets the underlying mechanism rather than the symptom alone. The etiology can be broadly categorized into metabolic, nutritional, toxic, mechanical, hereditary, and idiopathic origins .

Metabolic and Endocrine Disorders

Diabetic neuropathy stands as the most prevalent cause of burning feet syndrome globally. Up to 50% of individuals with diabetes mellitus develop some form of peripheral neuropathy, with sensory-predominant small fiber involvement frequently manifesting as burning pain . Chronic hyperglycemia induces oxidative stress, advanced glycation end-product accumulation, and microvascular ischemia, collectively damaging peripheral nerve fibers.

Hypothyroidism represents another endocrine contributor. Untreated thyroid hormone deficiency can lead to peripheral neuropathy through mucopolysaccharide deposition in nerve tissues and altered nerve conduction velocities . Similarly, **chronic kidney disease** and uremia result in toxic metabolite accumulation that impairs nerve function, particularly in dialysis-dependent patients .

Nutritional Deficiencies

The role of B-complex vitamins in nerve health cannot be overstated. Deficiencies in **thiamine (B1), riboflavin (B2), pyridoxine (B6), and cobalamin (B12)** have all been implicated in BFS pathogenesis . Vitamin B12 deficiency, in particular, is increasingly recognized in older adults, strict vegetarians, and patients with autoimmune conditions such as Crohn’s disease or pernicious anemia . Chronic alcoholism compounds this risk through direct neurotoxicity and malabsorption.

Toxic and Pharmacological Causes

Numerous medications can induce peripheral neuropathy and burning feet. **Chemotherapeutic agents, antiretroviral nucleoside reverse transcriptase inhibitors,**

metronidazole, isoniazid, statins, amiodarone, and even excessive vitamin B6 supplementation have been documented as culprits. Environmental toxins such as lead and mercury may also precipitate neuropathic symptoms.

Mechanical and Entrapment Neuropathies

Tarsal tunnel syndrome, involving compression of the posterior tibial nerve, and **Morton's neuroma**, characterized by thickened plantar digital nerve tissue, can produce localized burning sensations. Prolonged pressure from ill-fitting footwear, repetitive trauma, or abnormal gait mechanics may exacerbate these conditions.

Hereditary and Idiopathic Variants

Recent literature has highlighted **autosomal dominant burning feet syndrome** and genetic mutations affecting nerve transmission as potential causes in familial cases. Idiopathic BFS—where no cause is identified despite extensive evaluation—remains a diagnostic challenge and may involve neuroinflammatory or psychosomatic pathways.



Burning Feet Illustration

Figure 1: Conceptual illustration depicting the burning sensation characteristic of Grierson-Gopalan syndrome. The symptoms often localize to the plantar surface but may extend to the dorsum of the feet and lower legs.

Pathophysiology: From Nerve Fiber to Sensory Perception

The pathophysiology of Grierson-Gopalan syndrome hinges on the dysfunction of peripheral nerve fibers, particularly **small unmyelinated C fibers** and **thinly myelinated A δ fibers** responsible for nociception and temperature sensation.



In diabetic and alcoholic neuropathy, chronic metabolic insults lead to **distal axonopathy**, where the longest nerve fibers—those supplying the feet—degenerate first. This “dying-back” phenomenon explains the characteristic stocking-glove distribution of symptoms. Damaged nerve fibers become hyperexcitable, generating ectopic action potentials that the brain interprets as burning pain in the absence of external thermal stimuli .

Recent case studies have reinforced the central role of **small fiber neuropathy (SFN)** in BFS. A 2025 case report described a 71-year-old male with bilateral burning feet, normal proprioception, yet impaired temperature and pinprick sensation—classic for SFN . Unlike large fiber neuropathies, SFN often evades conventional nerve conduction studies, necessitating specialized diagnostic approaches such as skin biopsy with intraepidermal nerve fiber density assessment .

Vascular mechanisms also contribute. In **peripheral artery disease (PAD)**, reduced arterial inflow causes ischemic rest pain, particularly severe in the plantar arches at night. The resulting hypoxia sensitizes nociceptors and perpetuates the burning sensation .

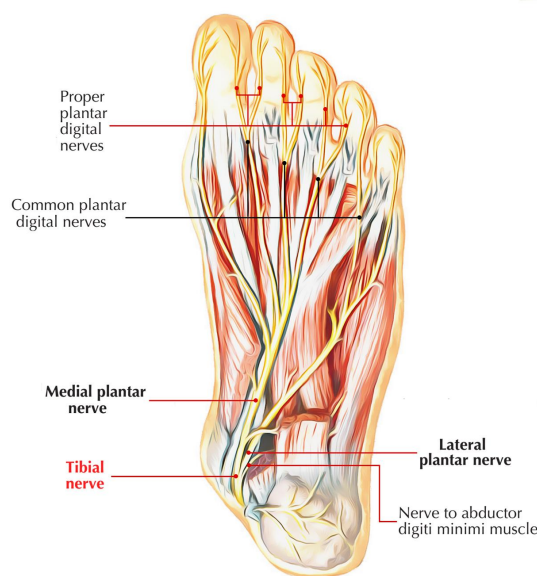
Clinical Features: Beyond the Burn

The hallmark of Grierson-Gopalan syndrome is, unsurprisingly, a burning sensation in the feet. However, the clinical picture is often richer and more nuanced, encompassing a spectrum of sensory disturbances that can significantly impair quality of life .

Patients typically describe the burning as beginning in the **soles of the feet**, sometimes ascending to involve the dorsum, ankles, or lower legs. The sensation is frequently accompanied by **tingling (paresthesia)**, **pins-and-needles**, **numbness**, or a **dull, heavy ache**. A defining characteristic is **nocturnal exacerbation**—symptoms often intensify at night, disrupting sleep and creating a cycle of fatigue and heightened pain perception .

Physical examination may reveal **erythema** and **warmth** of the overlying skin in some patients, though many present with entirely normal dermatological findings. Importantly, **neurological examination is often unremarkable** in terms of motor function: muscle strength is preserved, deep tendon reflexes may be intact or mildly diminished, and there are no upper motor neuron signs such as extensor plantar responses . This dissociation between severe subjective symptoms and relatively benign objective findings can lead to diagnostic skepticism.

Some patients report **hyperesthesia**—exquisite sensitivity to touch—where even the weight of bed sheets becomes intolerable. In advanced cases, particularly diabetic neuropathy, **loss of protective sensation** may coexist paradoxically with burning pain, predisposing to foot ulcers and Charcot arthropathy .



Plantar Nerve Anatomy

Figure 2: Anatomical diagram of the plantar nerves of the foot. The medial and lateral plantar nerves, branches of the tibial nerve, innervate the sole and are frequently implicated in entrapment neuropathies and metabolic peripheral neuropathies underlying BFS.

Diagnostic Approach: Unraveling the Cause

Diagnosing Grierson-Gopalan syndrome is primarily a clinical endeavor, yet a structured investigative approach is essential to uncover the underlying etiology and exclude mimics .

Clinical Assessment

The diagnostic journey begins with a meticulous **history**: characterizing the onset, duration, diurnal variation, and alleviating or aggravating factors of the burning sensation. Clinicians should probe for comorbidities such as diabetes, thyroid disease, alcohol use, medication history, and family history of neuropathy. The **physical examination** focuses on sensory testing (light touch, pinprick, vibration, proprioception), reflexes, motor strength, and vascular assessment of the lower limbs .

Laboratory Investigations

Baseline blood work typically includes **fasting glucose and HbA1c**, **thyroid function tests**, **complete blood count**, **renal function**, **liver enzymes**, **vitamin B12 and folate levels**, and **serum uric acid** . Additional tests such as serum protein electrophoresis, HIV serology, and autoimmune panels may be warranted based on clinical suspicion.

Electrophysiological Studies

Nerve conduction studies (NCS) and **electromyography (EMG)** are valuable for detecting large fiber neuropathy but may be normal in pure small fiber involvement . When SFN is suspected, **quantitative sensory testing (QST)** and **skin biopsy with intraepidermal nerve fiber density (IENFD)** analysis offer greater sensitivity .



Imaging and Specialized Tests

If entrapment neuropathy or structural lesions are suspected, **MRI** or **ultrasound** of the ankle and foot may be indicated. In rare, atypical cases, **nerve biopsy** may be considered . Psychiatric evaluation is recommended for idiopathic cases to assess psychosomatic contributions .

Table 1: Etiological Classification of Grierson-Gopalan Syndrome

Category	Specific Causes	Mechanism
Metabolic/Endocrine	Diabetes mellitus, hypothyroidism, chronic kidney disease, hyperuricemia	Metabolic toxicity, microvascular ischemia, toxin accumulation
Nutritional	Vitamin B1, B2, B6, B12 deficiencies; malabsorption syndromes	Impaired nerve metabolism, demyelination
Toxic/Pharmacological	Alcohol, chemotherapy, isoniazid, metronidazole, statins, excess B6	Direct neurotoxicity, axonal degeneration
Mechanical	Tarsal tunnel syndrome, Morton's neuroma, trauma, ill-fitting footwear	Nerve compression, entrapment, repetitive microtrauma
Hereditary	Autosomal dominant BFS, Charcot-Marie-Tooth disease	Genetic mutations affecting nerve structure/function
Infectious/Inflammatory	HIV/AIDS, leishmaniasis, multiple sclerosis	Immune-mediated nerve damage, direct infection
Vascular	Peripheral artery disease	Ischemic hypoxia of nerve tissues
Idiopathic	No identifiable cause after extensive evaluation	Presumed neuroinflammatory or genetic mechanisms

Table 2: Diagnostic Workup for Burning Feet Syndrome

Investigation	Purpose	Clinical Indication
Fasting glucose, HbA1c	Detect diabetes/prediabetes	All patients with BFS
Thyroid function tests (TSH, T3, T4)	Identify hypothyroidism	Symptoms of fatigue, cold intolerance, weight gain
Vitamin B12, folate	Detect nutritional deficiency	Vegetarians, elderly, malabsorption history



Investigation	Purpose	Clinical Indication
Serum creatinine, eGFR	Assess renal function	Known kidney disease, uremic symptoms
Liver function tests	Detect hepatic dysfunction	Alcohol use, medication toxicity
Nerve conduction studies/EMG	Evaluate large fiber neuropathy	Objective sensory/motor deficits
Skin biopsy (IENFD)	Diagnose small fiber neuropathy	Normal NCS with burning pain
MRI/Ultrasound of foot/ankle	Identify entrapment/structural lesions	Focal symptoms, suspected tarsal tunnel
Psychiatric evaluation	Assess psychosomatic factors	Idiopathic cases, anxiety/depression history

Differential Diagnosis

Several conditions can mimic Grierson-Gopalan syndrome, and distinguishing them is critical for appropriate management.

Erythromelalgia shares remarkable overlap, featuring burning pain, erythema, and warmth of the extremities. However, erythromelalgia is often triggered by heat or exercise and relieved by cooling, whereas BFS typically worsens at night regardless of ambient temperature .

Complex regional pain syndrome (CRPS) follows trauma and is associated with autonomic changes, allodynia, and trophic skin changes beyond the sensory symptoms of BFS .

Restless legs syndrome (RLS) causes nocturnal leg discomfort but is characterized by an irresistible urge to move rather than a pure burning sensation .

Peripheral artery disease causes ischemic rest pain, but this is often relieved by dependency of the limb and associated with absent pulses and bruits .



Burning Feet

Neuropathy

Figure 3: Clinical representation of burning feet with erythema. While some patients exhibit visible skin changes, many present with normal examination findings despite severe subjective symptoms.

Management and Treatment

The management of Grierson-Gopalan syndrome is inherently **multimodal and etiology-directed**. There is no universal cure; rather, therapy aims to halt progressive nerve damage, alleviate symptoms, and restore functional quality of life .

General and Conservative Measures

For all patients, conservative strategies form the foundation of care. **Cool water foot soaks** (15 minutes) can provide temporary relief. Patients are advised to wear **breathable cotton socks, open-toed or well-ventilated footwear**, and to **elevate the feet** when possible. Sleeping in a **cool room** (65–68°F) may reduce nocturnal symptom severity .

Pharmacological Management

When conservative measures prove insufficient, pharmacotherapy is introduced. The choice of agent depends on symptom severity, comorbidities, and patient tolerance.

Neuropathic pain modulators such as **gabapentin** and **pregabalin** are first-line options, reducing ectopic neuronal firing. **Tricyclic antidepressants** (amitriptyline, desipramine) and **serotonin-norepinephrine reuptake inhibitors** (duloxetine, venlafaxine) address both pain and



associated sleep disturbance . **Anticonvulsants** (carbamazepine, topiramate) may benefit select patients.

Topical agents offer localized relief with minimal systemic effects. **Capsaicin cream** depletes substance P from nociceptive fibers, while **lidocaine patches** provide sodium channel blockade . For burning feet secondary to athlete's foot, **topical antifungals** (terbinafine, miconazole) are curative .

Disease-Specific Interventions

Treating the underlying cause often yields the most durable results. **Glycemic control** in diabetes, **thyroid hormone replacement** in hypothyroidism, **vitamin B12 supplementation** in deficiency, and **alcohol cessation** in alcoholic neuropathy are paramount . For **hyperuricemia-associated BFS**, allopurinol may be beneficial .

Procedural and Emerging Therapies

In refractory cases, interventions such as **sympathetic ganglion blocks**, **spinal cord stimulation**, **transcranial magnetic stimulation**, and **botulinum toxin injections** have been explored, though evidence remains limited . Orthopedic surgery may be indicated for entrapment neuropathies unresponsive to conservative care .

Physical Therapy and Orthotics

Custom orthotics, gait retraining, and physical therapy can address mechanical contributors such as tarsal tunnel syndrome or Morton's neuroma by offloading compressed nerves and optimizing biomechanics .

Table 3: Pharmacological Management of Grierson-Gopalan Syndrome

Drug Class	Examples	Mechanism	Considerations
Gabapentinoids	Gabapentin, Pregabalin	Calcium channel $\alpha 2$ - δ ligand modulation	First-line; monitor for sedation, dizziness
Tricyclic Antidepressants	Amitriptyline, Desipramine	Inhibition of serotonin/norepinephr ine reuptake	Effective for nocturnal pain; anticholinergic side effects
SNRIs	Duloxetine, Venlafaxine	Dual neurotransmitter reuptake inhibition	Favorable in diabetic neuropathy; monitor blood pressure
Anticonvulsants	Carbamazepine, Topiramate	Sodium channel modulation	Alternative or adjunctive therapy
Topical Agents	Capsaicin, Lidocaine	Depletion of substance P; local	Minimal systemic effects;



Drug Class	Examples	Mechanism	Considerations
		anesthetic	initial burning with capsaicin
NSAIDs/Analgesics	Ibuprofen, Tramadol	Anti-inflammatory; opioid receptor agonism	Short-term use; tramadol for severe breakthrough pain
Vitamin Supplementation	B12, Thiamine, B-complex	Cofactor replacement	Curative in deficiency states; monitor levels

Prognosis and Quality of Life

The prognosis of Grierson-Gopalan syndrome is highly variable and intimately tied to the underlying etiology. In **nutritional deficiencies**, prompt supplementation can lead to complete resolution. In **diabetic neuropathy**, symptoms may stabilize with glycemic control but often persist as chronic pain. **Idiopathic cases** pose the greatest challenge, with many patients enduring years of discomfort despite exhaustive evaluation .

The syndrome exerts a profound toll on **quality of life**. Sleep disruption, anxiety, depression, and reduced mobility are common sequelae. The invisible nature of the pain—often dismissed by family, employers, and even healthcare providers—can compound psychological distress .

Current Research Gaps and Future Directions

Despite growing recognition, significant gaps persist in our understanding of Grierson-Gopalan syndrome. There is a striking **absence of large-scale epidemiological studies**, **no standardized diagnostic criteria**, and a **paucity of randomized controlled trials** evaluating treatment efficacy . Much of the existing literature comprises anecdotal reports, small observational studies, and case series with inherent geographic bias toward Asia and the Far East .

Emerging areas of interest include:

- **Genomic screening** for hereditary forms and mutations affecting nerve transmission
- **Neuroinflammatory biomarkers** to elucidate idiopathic cases
- **Advanced imaging techniques** to visualize small fiber pathology non-invasively
- **Procedural interventions** such as spinal cord stimulation and neuromodulation for refractory pain

A **multidisciplinary approach** integrating neurology, endocrinology, podiatry, pain medicine, and psychiatry is increasingly advocated as the optimal framework for managing this complex syndrome .

Conclusion

Grierson-Gopalan syndrome, or burning feet syndrome, stands at the intersection of neurology, metabolism, and chronic pain medicine—a condition as old as clinical medicine itself, yet still incompletely understood. From Grierson's initial observations in the 19th century to



modern insights into small fiber neuropathy and genetic predisposition, our conceptualization of BFS has evolved considerably. Yet the core clinical reality remains unchanged: patients suffering from an invisible fire, often dismissed, frequently undiagnosed, and desperately seeking relief.

The path forward demands greater clinical awareness, standardized diagnostic protocols, and rigorous research into both pharmacological and non-pharmacological interventions. For the clinician, BFS should serve as a diagnostic sentinel—a symptom that demands systematic investigation into diabetes, nutritional status, thyroid function, medication exposure, and nerve integrity. For the researcher, it represents a frontier where neuroinflammation, genetics, and nociception converge. And for the patient, it is a reminder that even the most subjective symptoms warrant compassionate, evidence-based care.

As our understanding of peripheral nerve biology deepens and personalized medicine advances, there is hope that the flames of Grierson-Gopalan syndrome may one day be extinguished—not merely masked, but truly cured.

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