International Journal of Women's Dermatology 7 (2021) 276–279

Contents lists available at ScienceDirect

International Journal of Women's Dermatology

Review

Idiopathic pure sudomotor failure: A review and two cases

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ARTICLE INFO

Article history:
Received 4 August 2020
Received in revised form 9 December 2020
Accepted 15 December 2020

Keywords:
Idiopathic pure sudomotor failure
IPSF
AIGA

ABSTRACT

Idiopathic pure sudomotor failure (IPSF) is a rare disease characterized by acquired impairment in total body sweating despite exposure to heat or exercise. Its etiology is unknown but thought to involve defective cholinergic receptors on eccrine sweat glands. This article reviews the epidemiology, pathophysiology, presentation, and management of IPSF. Additionally, we report two cases of IPSF treated with multimodal therapy, including stacked antihistamine regimens and omalizumab, resulting in symptom improvement. This is the first report of treatment of IPSF with omalizumab, although its benefit is uncertain and requires further study.

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Introduction

Idiopathic pure sudomotor failure (IPSF) is the most common form of acquired idiopathic generalized anhidrosis (AIGA), a group of syndromes that demonstrate acquired impairment in total body sweating despite exposure to heat or exercise (Munetsugu et al., 2017). IPSF can be distinguished from the two other subtypes of AIGA, sudomotor neuropathy and sweat gland failure, by the lack of abnormalities in the nerve fibers and sweat glands, respectively (Chen et al., 2008), although management is similar for all three subtypes (Munetsugu et al., 2017).

Herein, we review the epidemiology, pathophysiology, presentation, and management of IPSF. Also, we present two patients with IPSF with the goals of raising awareness of this condition and reporting on potential treatment strategies.

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https://doi.org/10.1016/j.ijwd.2020.12.011

Epidemiology

IPSF is either exceedingly rare, underreported, or both, and its prevalence is unknown. The majority of cases have been reported in Japan, and there is limited awareness of the condition in the United States (Kobayashi et al., 2014; Munetsugu et al., 2017; Nakazato et al., 2004; Ohshima et al., 2013; Suma et al., 2014). A survey of neurology and dermatology departments in Japan reported 145 cases of AIGA between 2010 and 2015 and found that AIGA predominantly affected younger men (126 of 145 patients were male [87%]; mean age of onset: 30.3 years [range, 1–69]; Munetsugu et al., 2017).

Another case series of 15 patients with AIGA at one institution in Singapore reported similar findings (14 of 15 patients were male [93%]; mean age of diagnosis: 28.5 years [range, 15–62 years]; Tay and Chong, 2014). Whether IPSF is truly more prevalent in men is unknown.

Pathophysiology

The etiology of IPSF remains unknown. Malfunctioning muscarinic cholinergic receptors on eccrine sweat glands are thought to play a role (Nakazato et al., 2004). The recent literature proposes autoimmune targeting of these receptors, preventing their response to acetylcholine stimulation (Munetsugu et al., 2017). Excess acetylcholine may stimulate sensory nerve terminals to cause pain, and in some cases it may also act on mast cells to cause cholinergic urticaria via the release of histamine (Nakazato et al., 2004).

Although most of the body contains eccrine sweat glands, which are innervated by cholinergic fibers, the axillae, palms, and soles are also supplied by apocrine glands, which are under adrenergic control. Well-preserved sweating from the axillae, palms, and soles with a lack of pain symptoms in those areas supports the role of disturbed cholinergic transmission in the pathogenesis of IPSF.

Clinical and histopathologic features

IPSF is characterized by generalized hypohidrosis that spares the palms and soles, severe heat intolerance, and burning pain on exposure to increased temperatures in the absence of other autonomic dysfunction. Because sweating assists in thermoregulation, patients with IPSF experience rapid rises in core temperature. IPSF is also associated with cholinergic urticaria, characterized by small and pruritic wheals over the entire body (Nakazato et al., 2004). Although spontaneous resolution occurs in some cases, patients often experience chronic, debilitating symptoms that severely affect their quality of life.

Serum IgE may be elevated in patients with IPSF (Munetsugu et al., 2017; Tay and Chong, 2014). Serum levels of carcinoembryonic antigen have been found to be elevated in patients with AIGA and may correlate with disease activity (Honma et al., 2015; Nakazato et al., 2016; Sano et al., 2017).

Skin biopsy may be helpful in distinguishing between IPSF and AIGA due to sweat gland failure but is not necessary for diagnosis (Munetsugu et al., 2017). Skin biopsy of IPSF typically reveals intact sweat glands and sometimes shows lymphocytic infiltration around sweat glands as assessed by light microscopy, but there may be no recognizable abnormalities (Munetsugu et al., 2017; Satoh, 2016).

Differential diagnosis

IPSF is a diagnosis of exclusion. Generalized anhidrosis can be classified first into acquired versus congenital, and thus congenital conditions (e.g., anhidrotic/hypohidrotic ectodermal dysplasia, insensitivity to pain with anhidrosis, and Fabry disease) should be excluded (Munetsugu et al., 2017). Next, acquired anhidrosis/hypohidrosis secondary to neuropathy, connective tissue disease (e.g., Sjogren syndrome), endocrinopathy and metabolic disorders, and drugs (e.g., anticholinergic agents) should be excluded (Munetsugu et al., 2017).

Anhidrosis or hypohidrosis, sparing the palms and soles, and association with cholinergic urticaria distinguish IPSF from other subtypes of AIGA. Skin biopsy may distinguish IPSF from sweat gland failure, and electron microscopy and autonomic fiber marker vasoactive intestinal peptide may distinguish IPSF from sudomotor neuropathy (Chen et al., 2008).

Management

Systemic corticosteroid therapy is recommended for the initial management of IPSF based on several successful case reports. The effectiveness of systemic steroids may be due to a potential autoimmune etiology of IPSF. Several authors have reported the use of steroid pulse therapy with or without additional intravenous or oral steroids to follow (Nakazato et al., 2004; Ohshima et al., 2013; Halioua et al., 2014; Kobayashi et al., 2014). There is no consensus on steroid dosing, but a common regimen is 1 to 2 courses of a 3-day intravenous infusion of methylprednisolone (500–1000 mg daily; Munetsugu et al., 2017). This modality has been found to be most effective in patients early in their disease course or with concurrent cholinergic urticaria, although this has not yet been studied in a randomized trial (Munetsugu et al., 2017). Steroids can offer immediate symptom relief and may induce long-term remission, but higher doses of steroids are required to control urticaria, and recurrence is not uncommon after steroid doses are tapered (Munetsugu et al., 2017).

Antihistamines may be considered for patients with steroid-resistant IPSF; histamine activity at H1 receptors inhibits acetylcholine-induced sweating and sudomotor activity (Munetsugu et al., 2017). Oral immunosuppressants may also be reasonable in patients who are unresponsive to or unable to use steroids. Cases of AIGA have been successfully treated with cyclosporine (Mok and Tey, 2018) or intravenous immunoglobulin (Halioua et al., 2014; Masuda et al., 2016).

Case 1

An athletic 31-year-old man with a history of mild atopic dermatitis (AD) and dermatographism presented with 10 years of episodic, sharp, pinprick pain over the entire body except for the palms and soles, triggered by exercise or an increase in ambient temperature. When his body warmed to trigger a sweat response, he would suddenly experience stabbing pain over most of his skin that was completely debilitating, and he would be paralyzed in pain for upward of an hour. He described the sensation as hundreds of ‘‘sharp needles” or ‘‘electric shocks.” Episodes were also triggered by exposure to the sun, spicy food, and emotional stimuli, but heat was by far the most common trigger.

The patient did not exhibit skin lesions during these episodes, but on physical examination, he did have evidence of mild AD with light eczematous plaques on the popliteal fossa, antecubital fossa, and neck. Erythrocyte sedimentation rate, C-reactive protein, C3, C4, anti-double stranded DNA, anti-Sjögren's syndrome-related antigen A and B autoantibodies, complete blood count, comprehensive metabolic panel, and celiac panel were within the normal limits. Punch biopsy of an AD plaque revealed spongiotic epithelial changes consistent with AD and a sparse infiltrate of lymphocytes and eosinophils around the eccrine glands, which had mild

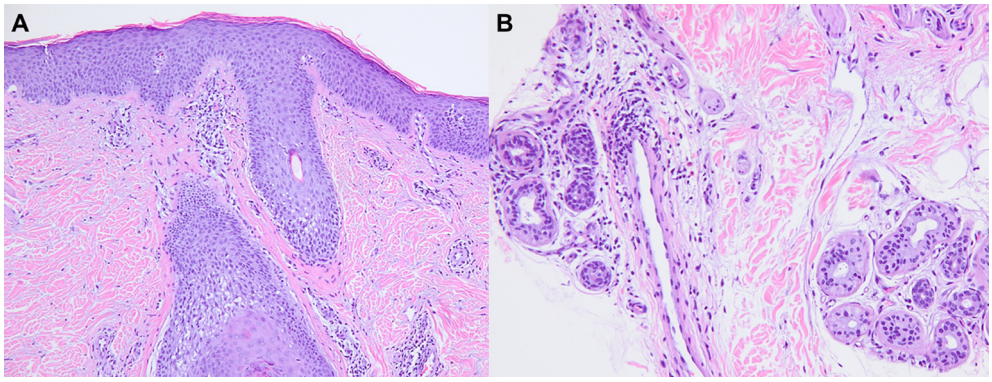

Fig. 1. (A, B) Punch biopsy demonstrated mild spongiosis in the epidermis and follicular epithelium, consistent with the patient's history of atopic dermatitis. A sparse infiltrate of lymphocytes and eosinophils is present around the eccrine glands, which have some mild irregularity in the epithelial cell organization.

irregularity in the epithelial cell organization (Fig. 1). The combination of pain, pruritus, and symptoms triggered by heat, coupled with perieccrine inflammation on biopsy, led to a diagnosis of IPSF.

The patient was started on a stacked antihistamine regimen, consisting of cetirizine 10 mg nightly, fexofenadine 180 mg daily, and ranitidine 150 mg twice daily. He concurrently started omalizumab 450 mg monthly given the association of IPSF with cholinergic urticaria. Finally, he began a low histamine diet and avoided spicy foods. The patient reported a subsequent decreased frequency of attacks. After four treatments of omalizumab, the patient discontinued because he believed that the efficacy of the therapy was not commensurate with its time and cost, and he began to focus on lifestyle changes, such as yoga, meditation, and temperature regulation during exercise. Two years after the initial presentation, the patient reported marked improvement; mild symptoms only appeared 1 in every 5 trips to the gym. He had not experienced debilitating pain in over 6 months.

Case 2

A 28-year-old pilot who had been deployed to Kuwait, where he worked in an aircraft with reported ambient temperatures >130°F, presented with widespread, burning pain that felt like pins and needles that worsened with heat, exercise, and even minor fluctuations in ambient temperature. He reported difficulty sleeping at night due to worsening of symptoms associated with the use of blankets. He noted involvement of the whole body, with sparing of the palms and soles. Symptoms were not worsened with any particular food. On physical examination, thin, pink, ill-defined papules were found scattered on the trunk and bilateral arms and thighs, consistent with mild AD. No frank urticaria was noted. The patient exercised at the clinic, doing three sets of three floors of stairs with no increase in his basal temperature, which remained at 96°F, and sweat was not visible on the patient's skin. Laboratory workup, including erythrocyte sedimentation rate, C-reactive protein, C3, C4, anti-double stranded DNA, anti-Sjögren's syndrome-related antigen A and B autoantibodies, and complete blood count, was unremarkable.

The patient attempted various topical therapies with no improvement. He did experience some improvement with a stacked antihistamine regimen, but he sought better control and thus attempted a trial of high-dose omalizumab, receiving 300 mg of omalizumab every 15 days, given the association of IPSF with cholinergic urticaria. He discontinued omalizumab after several months given its uncertain benefit. The patient also attempted acupuncture, Chinese herbal therapy, a course of high-dose steroids, pyridostigmine, and acetaminophen 325 mg once daily, with no clear benefit. At the most recent follow-up, he noted improvement in the burning and stinging symptoms and that he was beginning to sweat focally on the face and under the arms in addition to the palms and soles. He attested that "working through it slowly with exercise" has offered the most benefit.

Discussion

Herein, we report two cases of IPSF that were treated with multimodal therapy, including stacked antihistamine regimens and omalizumab, resulting in gradual improvement, although it is unclear which therapies led to the greatest benefit. We are the first to report treatment of IPSF with omalizumab, although both patients reported only mild improvement and did not continue this therapy long term.

Although not seen with our cases, IPSF commonly presents with cholinergic urticaria, for which a pathophysiologic link has been proposed (Nakazato et al., 2004). Specifically, the pathogenesis of cholinergic urticaria with hypohidrosis or anhidrosis, a subtype of cholinergic urticaria, may involve mast cell degranulation secondary to increased levels of acetylcholine due to reduced expression of cholinergic M3 receptors on eccrine sweat gland epithelial cells (Sawada et al., 2014). In contrast, the pathogenesis of the conventional sweat allergy-type of cholinergic urticaria likely involves IgE-mediated mast cell activation, and patients with IPSF lack sweat hypersensitivity (Fukunaga et al., 2018). Omalizumab has been used successfully to treat patients with cholinergic urticaria without comorbid IPSF and has not previously been reported for the treatment of IPSF (Altrichter et al., 2019).

Given the paucity of documented cases, clear diagnostic criteria and treatment modalities remain to be established for IPSF. Clinically, our patients exhibited several signs and symptoms that aided in the diagnosis of IPSF, especially prickling pain and pruritus in an eccrine distribution exacerbated by heat and exercise, which is most characteristic of the IPSF subtype of AIGA. Skin biopsy also helped establish the diagnosis in the first case, with mild perieccrine inflammation consistent with what has been previously reported for IPSF.

We treated our patients with a stacked antihistamine regimen, which has had moderate success in several documented cases (Munetsugu et al., 2017; Suma et al., 2014). An example of a stacked antihistamine regimen used in Case 1 is as follows. Start with 10 mg of cetirizine for the first week. If improvement is minimal, the patient should add 180 mg of fexofenadine the following week, then 150 mg of ranitidine or another H2 blocker the third week, and an additional 150 mg of ranitidine the fourth week. If the patient experiences improvement, the progression of the regimen should be halted, and the regimen should be maintained for an additional 3 months before discontinuation. Additionally, omalizumab can be considered for patients with IPSF similar to those with chronic recalcitrant urticaria (Nakazato et al., 2004).

Conclusion

We report on two cases of IPSF, a rare acquired disease characterized by generalized anhidrosis or hypohidrosis sparing the palms and soles, as well as pain and pruritus exacerbated by heat and exercise. Prompt recognition of this disease is needed to mitigate its debilitating effects on quality of life. Treatment typically involves steroids, and the short-term prognosis is good. Antihistamines and oral immunosuppressants may be considered for patients who do not respond to steroids or prefer steroid-sparing agents. Omalizumab was not clearly beneficial in our two cases despite IPSF's established association with cholinergic urticaria, and further study is needed to evaluate its potential efficacy for IPSF.

Conflicts of interest

None.

Funding

None.

Study approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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