Frontal Fibrosing Alopecia and Increased Scalp Sweating: Is Neurogenic Inflammation the Common Link?

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Introduction

Frontal fibrosing alopecia (FFA) is an uncommon scarring hair loss disorder that is characterized by a band-like recession of the frontal hair line that is often associated with eyebrow, face and body hair loss [1]. The condition is permanent as the hair follicles (HFs) in the zones of alopecia are progressively destroyed and replaced by scar-like fibrous tissue [2]. FFA was first described by Kossard [2] in 1994, and since then, the incidence of the condition appears to be increasing [3–7].

We present a series of patients with FFA and increased sweating predominantly localized to the scalp, and potential explanations for this association are discussed. We hypothesize that the reported increase in sweating seen in our patients may be in part related to the inflammatory process occurring locally within the skin, either inducing a local axonal sweating reflex or through direct modulation of sweat gland secretion by neuropeptides.

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## Table 1. Clinical summary of 11 patients with FFA and increased scalp sweating

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis Age, years</th>
<th>Sex</th>
<th>Menopause</th>
<th>PMH</th>
<th>Duration of hair loss</th>
<th>Clinical features</th>
<th>Sweating</th>
<th>Response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FFA (B) 69 F</td>
<td>Yes</td>
<td>Bilateral mastectomy for breast cancer; oesophagitis; hypothyroidism; amaurosis fugax</td>
<td>7 years</td>
<td>Frontal recession with associated itching, burning and a stinging sensation of the scalp, perifollicular erythema and hyperkeratosis on examination</td>
<td>Increased sweating in distribution of hair loss; different to normal sweat – thick and smelly; wakes at night with a drenched pillow</td>
<td>Previous HCQ and pioglitazone = failed No treatment planned</td>
<td></td>
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<tr>
<td>2</td>
<td>FFA (B) 75 F</td>
<td>Yes</td>
<td>Hypercholesterolaemia; cerebral haematoma</td>
<td>2 years</td>
<td>Frontotemporal hairline recession associated with itching of the scalp; symptoms were initially thought to be associated with statin therapy, but no change when stopping the treatment occurred</td>
<td>Severe sweating exactly over the area of hair loss; would leave scalp ‘dripping wet’, the sweating would occur anytime but was made worse by hot weather</td>
<td>Topical aluminium chloride (Driclor®) – some improvement in sweating Botulinum toxin injections (Botox®) = reduced sweating + itch within 2 weeks; also associated with reduced visible inflammation</td>
<td></td>
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<tr>
<td>3</td>
<td>FFA (B) 67 F</td>
<td>Yes</td>
<td>Systemic lupus erythematosus; bowel resection for ischaemic bowel secondary to diverticulosis</td>
<td>6 years</td>
<td>Slowly progressive recession of the frontal hairline associated with itching and erythema of the scalp; associated with generalised hair thinning</td>
<td>Two-year history of ‘drenching sweats’ over the entire scalp, worse over the frontotemporal region</td>
<td>Treatment with HCQ for the lupus was poorly tolerated and therefore discontinued Intermittent topical corticosteroids Botulinum toxin injections declined</td>
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<tr>
<td>4</td>
<td>FFA (M) 70 F</td>
<td>Yes</td>
<td>Asthma; eczema; rosacea</td>
<td>3 years</td>
<td>Recession frontal of temporal hairline; perifollicular erythema; no symptoms</td>
<td>Increased scalp sweating</td>
<td>Topical corticosteroids = no progression</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>FFA (M) 62 F</td>
<td>Menopause post-hysterectomy 20 years ago; HRT stopped due to s/e</td>
<td>Osteoporosis; OA; recurrent UTIs; low vitamin D; depression</td>
<td>10 months</td>
<td>3-year history of eyebrow loss; 10 months of frontal recession = progressive; scalp itch 2.5-cm recession from original hairline; perifollicular erythema; loss of eyebrows</td>
<td>Marked facial/scalp sweating</td>
<td>HCQ and doxycycline stopped due to s/e Gradual progression of hair loss</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>FFA + FPHL (M) 50 F</td>
<td>Menopause 7 years ago</td>
<td>Joint pain; high cholesterol</td>
<td>18 months</td>
<td>Progressive hairline recession; asymptomatic; loss of eyebrows 4-cm recession from original hairline; low-grade perifollicular erythema</td>
<td>Sweating in hair-bearing margin</td>
<td>Topical minoxidil, topical corticosteroids and HCQ – stable at follow-up</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>FFA (M) 54 F</td>
<td>F</td>
<td>Peri-menopausal hot flashes: increased scalp sweating</td>
<td>4–5 years</td>
<td>Always thin hair – progressive recession frontal hairline; occasional itch only; plucked eyebrows in past that never regrew 8-cm recession from original hairline; perifollicular erythema and scale</td>
<td>Scalp sweating</td>
<td>Progression despite lymecycline and HCQ</td>
<td></td>
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<tr>
<td>8</td>
<td>FFA (M) 64 F</td>
<td>F</td>
<td>Menopause 20 years ago; HRT on and off – hysterectomy and ovary removal</td>
<td>1 year</td>
<td>FFA and FPHL; recession = progressive; loss of eyebrows; asymptomatic 6.5-cm from original hairline; low-grade perifollicular erythema</td>
<td>Profuse facial and scalp sweating; no underlying cause identified Sweating worse with HCQ but improved with intralesional corticosteroids</td>
<td>Intralosomal corticosteroids; topical corticosteroids Lymecycline improved sweating with intralesional steroid injections</td>
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Description of Cases

All patients were identified retrospectively from two specialist hair clinics (Manchester and Brighton). The diagnosis of FFA was confirmed by clinical evaluation (fig. 1a) and scalp biopsy. Each patient complained of increased sweating of the scalp, in some cases specifically localized to the area of alopecia. The sweating was sufficiently troublesome for patients to proffer the symptom without direct questioning. In 2 females, the sweating was of such severity that they would sleep on a towel each night to absorb excess sweat. In 1 case treated with localized botulinum toxin injections to the scalp, not only did sweating improve but reduction in itch and diminished visible inflammation was also observed. Clinical details for each patient are presented in Table 1.

Discussion

Sweat is produced by eccrine sweat glands of which humans have several million distributed over nearly the entire body surface, with the palms, soles and scalp having the highest density. Each eccrine sweat gland consists of a secretory coil deep in the dermis and a duct that conveys the secreted sweat to the skin surface. Traditionally, the sweat gland is viewed as anatomically separate from the pilosebaceous unit; however, a recent morphological study suggests a much closer physical association with the HF, with the secretory coil consistently situated below the insertion of the arrector pili muscle close to the outer root sheath [8]. The primary function of the eccrine unit is thermoregulation, which is accomplished through the skin's cooling effects of evaporation of sweat from the skin's surface. Sweating is a reflex function that is controlled by the sympathetic nervous system. Stimulation of the sympathetic nervous system activates the sweat glands to produce sweat.

Sweat can be classified in a number of ways including: (1) whether this process only affects sweating or occurs as part of a wider disease process ('primary' or 'secondary'); (2) according to the distribution of sweating ('generalized' or 'focal'), or (3) according to the source of neural impulse ('cortical', 'hypothalamic', 'medullary', 'spinal cord' or 'local axon reflex'). For example, localized hyperhidrosis affecting the palms, soles and/or axillae (a presentation most familiar to dermatologists) would be classified as a primary, focal and cortical hyperhidrosis. A local axon reflex occurs when a stimulus applied to one branch of a nerve sets up an impulse that moves centrally to the point of division of the peripheral nerve, resulting in activation of sweat glands in other parts of the body, including the scalp.

All text and images are from the same source, and no external content is required to understand the context and meaning of the document. The document is a medical report discussing frontal fibrosing alopecia (FFA) and its associated sweating, with a focus on clinical cases and discussion of sweat physiology and classification.
of the nerve where it is then reflected back down the other branch to the effector organ. It is a peripheral reflex that bypasses higher integration centres in the central nervous system. Blood vessels, sweat glands and mast cells are most important effectors of local axon reflexes affecting the skin.

FFA was first described by Kossard [2] in 1994 and is generally regarded as a variant of lichen planopilaris (LPP) based on similarity in lesion morphology and indistinguishable histological features [3, 4]. A key event in the permanent HF loss seen in lesional FFA is the destruction of epithelial HF stem cells [2, 10], likely due to a Th1-biased inflammatory response and loss of HF immune privilege [11]. However, it is still unclear what predisposes to this inflammatory attack; genetic susceptibility may be important, whereas environmental factors may explain the recent identification, pattern and growing incidence of the condition [12].

One hypothesis for the pathogenesis of scarring alopecias is neurogenic skin inflammation [2]. Evidence for this comes from animal models where stressed mice show increased expression of neuropeptides (including substance P), increased degranulation of mast cells, and loss of HF immune privilege [13–17]. Further, we know that in mice, nerve-derived hedgehog signaling maintains a subset of bulge stem cells expressing Gli1, suggesting a vital role of nerve signaling in supporting HF stem cell function [18]. In humans, total numbers of mast cells along with the proportion of degranulating mast cells are increased in the peri-follicular bulge region in LPP/FFA [19]. Early work examining nerve fibre density and expression of substance P and cGRP in FFA is currently limited to meeting proceedings (i.e. unpublished) but suggests variability in the expression of these neuropeptides between lesional and non-lesional scalp skin as well as differences between LPP and FFA disease groups [20].

In the clinic, many patients cite stress as a potential trigger for their hair loss [21]. Interestingly, many of these neurogenic skin inflammatory signals, particularly substance P and cGRP, are also important in sweat regulation [22]. We hypothesize that the reported increase in sweating seen in our patients may be in part related to the inflammatory process occurring locally within the skin, either inducing a local axonal sweating reflex or through direct modulation of sweat gland secretion by neuropeptide effects.

In 1 patient who responded to anti-sweating therapy in the form of botulinum toxin injections, improvements in scalp itch and visible inflammation were also observed. In a separate patient, the excess sweating improved with anti-inflammatory measures in the form of corticosteroid injections into the affected scalp skin. These observations highlight the potential interaction between (neurogenic) inflammation and sweating and suggest possible avenues for future therapy development (e.g. botulinum toxin injections, topical capsaicin, etc.). The role of neurogenic inflammation (and botulinum toxin therapy) has been proposed in a number of other inflammatory conditions, including psoriasis [23, 24].

Another observation of note is the histological identification of dilated eccrine glands seen in 1 patient (fig. 1b). Eccrine gland changes are not well described in cicatricial alopecia, but it is likely that any change to these glands would represent a secondary phenomenon from either localized blockage of drainage (e.g. induced by localized fibrosis/inflammation) and/or gland atrophy (e.g. through inflammation-induced apoptosis/pressure effects). Interestingly, a number of reports describe the
presence of syringomas in scalp biopsies for hair loss, including cases of cicatricial alopecia, although whether these are truly associated or just represent a coincidental finding requires further study (see Deen et al. [25] for a review of the literature).

Although the above arguments plausibly explain the apparent association between increased sweating and FFA, the following should also be considered: (1) coincidence: do these patients just have a localized primary hyperhidrosis or even just physiological levels of sweating, which has become more evident due to the loss of hair? Eyebrow loss in FFA means that sweat is no longer prevented from falling into the eyes, and wet hair exaggerates the appearance of the hair loss, with both features drawing attention to the sweating; or (2) menopause effects: all patients described here are post-menopausal women with a few also experiencing increased face and/or body sweating in addition. However, other menopausal symptoms were generally absent (except hot flashes in 1 patient), and many were already well past the peri-menopause period at the time when symptoms typically began [26]. Further, FFA is recognized to also affect face and body hair growth by the same process as on the scalp [7, 27].

We present 11 women with FFA and associated scalp sweating. We propose that the mechanism for this may be through neurogenic inflammation and changes to localized neuropeptide signaling regulating sweating responses. Due to the retrospective nature of case identification and reliance on the patients providing information about their sweating unprompted, it is possible that increased sweating may in fact be more common than this report suggests (e.g. 8 of 116 FFA patients in the Manchester cohort) and should in future be specifically enquired about. Further work is required to confirm this potential association by objective quantification of hyperhidrosis and exploration of the underlying mechanisms, with particular focus on the role of neurogenic skin inflammation.

Acknowledgements

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Statement of Ethics

As the study presents a retrospective case, no ethical approval is required.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References


