Pruritus Ani

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Happiness is having a scratch for every itch.
Ogden Nash
American 20th Century Poet
Died 1971 of complications related to Crohn's Disease.

Introduction

Pruritus ani, in its worst form, is a miserable affliction. It is common; however, there is a spectrum of symptom severity and those falling into the severe category are rare. The majority of patients experience nothing more troubling than a transient 'itchy bottom'. Simple measures are usually all that are required to relieve suffering, and their physician is not consulted. Other patients with more persistent symptoms present to the proctologist who is confronted then with a difficult problem and a long list of differential diagnoses to consider and investigate.

Biology of Itch

Itch can be defined as an unpleasant cutaneous sensation associated with an urge to scratch. It is more or less voluntary, yet can very often be a subconscious motor activity [1].

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The sensation of itch may have evolved in order to protect the skin from agents (e.g. parasites, plant toxins) that would potentially breach its barrier to harm the organism. In this way, the itch response has similarities to the pain response, and indeed itch (pruriceptive) and pain (nociceptive) pathways seem to have evolved in tandem.

However, the two have differences. Whereas the sensation of pain causes reflex withdrawal away from the source of pain in an attempt to avoid the agent, itching causes an opposite response, that being to scratch, perhaps in an attempt to rid the skin of an agent that has already breached the skin's defences.

Pruriceptive and nociceptive pathways have evolved in order to provide us with potential survival benefits. As with other body systems that have evolved over generations, the pruriceptive system can become maladaptive in a number of individuals. This is usually in response to one or more causative agents, manifesting as miserable, intractable itching [1].

Itch is generated by specialised, itch-dedicated, cutaneous unmyelinated C fibres that have dense sensory nerve endings. These are distinct from the polymodal nociceptor mechanoreceptors involved in pain signalling as they do not respond to heat, mechanical or chemical stimuli. They show a sustained response to histamine which is a potent pruritogen and express the cell membrane receptor transient receptor potential cation channel subfamily V member 1 (TrpV1), also known as the capsaicin receptor [2].

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Pruriceptive fibres ascend the spinothalamic tract into the thalamus which in turn has projections into the cerebral cortex. Spinal and higher cortical projections interact with ascending fibres, and it is hypothesised that these projections attenuate the itch signal, much like the gating mechanism that exists for pain perception. Ikoma et al. have written an excellent and comprehensive review on the neurobiology of itch [3].

On a behavioural level, patients undergo a vicious itch-scratch-itch cycle. A pruritogen causes the skin to itch. The itch drives a scratch reflex. Scratching traumatises the skin and induces pain. Pain in turn suppresses itch for a length of time but the skin damage stimulates the release of pruritogenic inflammatory mediators leading to further itching and scratching and so on ad infinitum. The desire to scratch can be denied as there is a degree of higher cortical control over motor function; however, a stronger and stronger desire to satisfy the urge to scratch develops until the sufferer must relent. What follows is a vigorous and traumatising episode of scratching that produces a feeling that can be described as a combination of guilt, pain and exquisite pleasure. These symptoms are not confined to daylight hours. Patients often wake from sleep to find their fingernails bleeding, having traumatised their skin by scratching vigorously during sleep.

Pruritus Ani

Pruritus may be a reflection of an underlying systemic disease, a primary dermatological illness, a psychiatric or behavioural problem or a condition affecting the anorectum [4]. These causes and their various management options are discussed in detail elsewhere in this book but are summarised in Box 21.1. If investigation reveals no specific condition to be causing their symptoms, the patients are diagnosed as having idiopathic pruritus ani, a notoriously difficult and depressing condition to contend with, both as a patient and as that patient's physician. This chapter will deal specifically with idiopathic pruritus ani (IPA).

Box 21.1 Infective

Bacterial

Staphylococcus aureus, beta haemolytic streptococcus, *Corynebacterium minutissimum*, lymphogranuloma venereum, syphilis, tuberculosis, actinomycosis

Viral

Herpes simplex, herpes zoster, cytomegalovirus, human immunodeficiency virus, molluscum contagiosum, condylomata acuminata (papillomavirus)

Fungal

Candida albicans

Parasitic

Enterobius vermicularis (oxyuriasis, pinworm), Schistosomiasis cutis, *Sarcoptes scabiei* (scabies)

Neoplastic

Squamous cell carcinoma, basal cell carcinoma, Bowen's disease, extra mammary Paget's disease, melanoma, mycosis fungoides

Dermatoses

Psoriasis, lichen planus, seborrhoeic dermatitis, atopic dermatitis, erythema multiforme, systemic lupus erythematosus, amyloidosis, radiation dermatitis, lichen sclerosus et atrophicus, contact dermatitis, allergic dermatitis, scleroderma

Contact irritant

Drugs (e.g. IV steroid), topical applications, soap and cosmetics, clothing, detergents, latex

Anorectal

Fistula in ano, diarrhoeal illness, fissure in ano, haemorrhoids, gutter deformity, primary or secondary sphincter dysfunction, fibroepithelial polyp, villous adenoma, rectal or anal malignancy, postanal canal surgery

Systemic disease

Liver disease, renal failure, polycythemia rubra vera, diabetes mellitus, leukaemia

Psychological

Depression, psychosomatic illness, obsessive-compulsive disorder

Idiopathic Pruritus Ani

The true incidence of IPA is difficult to establish but in general is considered to be common albeit with a wide spectrum of severity. Men are afflicted more than women in a ratio of 4:1 [5].

A number of theories have been postulated in an attempt to describe an aetiological cause for pruritic symptoms.

Dietary

Specific dietary factors have been reported as important as a causative factor that once removed sees resolution of symptoms [6]. There is, however, little robust evidence for this and reports are largely anecdotal. Caffeine in particular has been reported as an irritant as well as being reported to cause transient weakness in the anal sphincter after its ingestion [7, 8]. In this, there may be an explanation for pruritic symptoms in the setting of subclinical incontinence (see next section).

Faecal Contamination

Poor perianal hygiene has been implicated as a cause of pruritus ani [7]. In an elegant experiment, Caplan applied autologous faeces to the perianal and underarm skin of a group of patients with ($n=12$) and a group of patients without ($n=15$) pruritus ani. A further group ($n=10$) had topical faecal application simulated to act as control [9].

Twelve of 27 of these subjects complained of perianal itching with an onset between 1 and 6 h of faecal application to the perianal skin. Four of these subjects had a history of pruritus ani, eight had no prior history. None of the control group suffered symptoms. Pruritus was instantly relieved with cleansing. A single subject developed pruritus on application to the arm. The conclusion of the study was that faeces acted as an irritant rather than an allergen.

Farouk studied rectal and internal anal sphincter pressures in a group of pruritus ani patients [10]. Those with pruritus had higher rectal pressures with lower internal anal sphincter pressures and prolonged internal sphincter relaxation than the control group. Pruritus was reported within an hour of the abnormal internal sphincter relaxation. The authors' conclusion was that occult faecal leakage was a cause of pruritus secondary to abnormal internal sphincter relaxation.

Given the above findings, chronic leakage of irritant faeces causing itch with subsequent mechanical skin trauma makes an interesting hypothesis. If indeed this is the case, symptoms may be amenable to treatment with a stool thickener such as loperamide. No trial data have been presented to support the hypothesis although anecdotally this approach can be successful.

Infective

The perianal region is subject to the same skin commensals as the remainder of the body. Due to its anatomy within the warm, moist gluteal folds and at the outlet from the gastrointestinal tract, additional flora may exist and thrive. Bacterial, viral, fungal and parasitic organisms all have been implicated as an aetiology; therefore, thorough investigation with swab, scraping and Wood's light examination is essential. Sexually transmitted infection is common and therefore appropriate questioning on history taking is essential.

Contact Dermatitis and Occult Perianal Dermatology

Dasan reports an interesting series of consecutive patients presenting to a combined dermatological and coloproctological clinic [11]. Out of 40 patients, 2 were identified as suffering from an anorectal condition that required surgical intervention. Thirty-four out of 40 patients were suffering from an underlying dermatosis, treatment of which improved or resolved their symptoms. Patch testing was undertaken in 32 out of 40. Eighteen of these patients showed hypersensitivity to allergens which are commonly found in remedies for pruritus ani. A patient was found to be sensitive to an ingredient of his wife's shampoo. Symptoms resolved on cessation of her practice of washing her hair in their shared bath water.

Patch testing as a useful instrument in the investigation of chronic pruritus ani is supported by Harrington who tested 80 patients with PA [12]. Fifty-five of these patients were patch test 'positive', 38 of them for a medication commonly used as a remedy for pruritus. As well as topical preparations, the advice to use 'wet wipes' is commonly given to patients in the clinic. Ingredients of wet wipes are occasionally allergenic on patch testing [13] and should be avoided.

Underlying Proctological Disease

Daniel et al. report in their series of 109 patients with pruritus ani that 75 % of these had an underlying coloproctological disorder: 20 % had haemorrhoids and 12 % had anal fissures; however, 19 % had an underlying coloproctological malignancy (11 % rectal cancer, 6 % anal cancer, 2 % colonic cancer) [7]. It is interesting to note this group's definition of chronic pruritus ani as being a condition with symptoms lasting over 6 weeks. Mentes' group had a median symptom length of 24 months [14]. Underlying anorectal conditions, whilst clearly important to exclude and treat if appropriate, do not seem to be as prevalent in other groups investigating idiopathic pruritus ani with a longer time course [11, 14–16].

Approach to Idiopathic Pruritus Ani

Having gone through appropriate examination, diagnosis and management of any identifiable cause of pruritus, a proportion of patients will remain symptomatic. These patients are defined as having idiopathic pruritus ani and can be challenging to manage.

Goligher's feelings towards pruritic patients were highlighted in Sagar's paper [15]:

> …a rectal clinic is apt to be haunted by its pruritic patients.. the peri-anal skin may be painful even to look at.. the itch has a tormenting, distracting character.. pain by comparison is almost a pleasure.. a bizarre form of auto-eroticism may result.. it is difficult to be enthusiastic about its treatment.

The clinician is hampered by a lack of knowledge regarding the underlying aetiology of this affliction and lacks a universally acceptable and easily deployed treatment that will alleviate the relentless suffering experienced by these patients. When faced with a pruritic patient in the clinic, therefore, the frustration of seeing such an individual is understandable.

However, some treatments that are generating interest and displaying promise have come to light since Goligher issued his statement.

Topical Capsaicin

Capsaicin is a biochemical extracted from red chilli peppers that has found success in the management of chronic pain. It is the active ingredient that puts the 'heat' into curries or other spicy foods. Its mechanism of action, although not completely understood, suggests that it plays a role in reducing substance 'p' concentrations from presynaptic neurones. Substance 'p' is an important sensory neuropeptide that may be responsible for transmission of signals along 'itch'-specific, type 'C' sensory neurones [17].

At its standard topical dose of 0.025 %, capsaicin causes an intense burning sensation when applied topically. This sensation prevents its use on perianal skin as the pain is poorly tolerated. Lysy's group felt that capsaicin may still have a role to play in the treatment of pruritus ani, albeit at an attenuated dose. By diluting the concentration, they were able to demonstrate that it was in fact tolerable to most patients and, when compared to a menthol ointment preparation, was effective as a treatment [18].

In their study, Lysy et al. studied 44 patients who had been diagnosed as having idiopathic pruritus ani. These patients underwent a double-blind, placebo-controlled crossover trial of capsaicin (0.006 %) ointment versus a menthol ointment as a placebo, each applied three times daily. Each arm of the trial lasted 4 weeks. Outcomes were measured on the basis of a symptom diary.

Results of the trial report that 31/44 patients experienced relief of itching with capsaicin versus 0/44 with placebo ($p < 0.0001$). For 24 of

these patients, relief was achieved within 24 h of commencing treatment, the remaining 7 experiencing relief within 72 h.

Long-term follow-up was achieved for 18 patients. Remission from symptoms was achieved with regular application every 2–3 days. Relief was either complete (4/18) or almost complete (14/18). Loss of effect was experienced in two patients who responded to increasing the concentration of the topical ointment to 0.012 %.

All patients experienced a 'burning' sensation as a side effect. Four patients were so intolerant of this symptom that they were unable to complete the trial. One patient developed urticaria and also was excluded. The burning sensation diminished with prolonged application.

Intradermal Methylene Blue Injection (Anal Tattooing Procedure) as a Treatment for Idiopathic Pruritus Ani

Methylene blue was the first synthetic drug and has found a variety of uses in medicine and industry over the last 120 years. Schirmer et al. present an excellent summary of the history, biochemical properties and various clinical applications of methylene blue [19].

In 1973, Yaacov Wolloch made a chance discovery of a technique involving local subcutaneous injection of methylene blue as a treatment for pruritus ani. The source was Rygick's 'Atlas of the operations on the rectum and colon' which was published in the former USSR. As the technique appeared to be straightforward, Wolloch and Dintsman adopted it and reported complete success in the treatment of 8 of 9 patients suffering from IPA in 1979 [20]. Their method involved outpatient treatment under local injection of 2 % procaine infiltration followed by the subcutaneous infiltration of 15–20 ml of 15 % methylene blue solution. The only reported side effect was a transient pyrexia in a single patient.

The technique continued to be unreported in the literature until Eusebio, Graham and Mody reported their experience between 1979 and 1989 on 21 patients with IPA. After 9.5 years of follow-up, recurrence was noted in 4 patients [21].

Initially, a mixture of 30–40 ml of 0.25 % Marcaine with 1:200,000 epinephrine was infiltrated, followed by 30 ml of 0.5 % methylene blue when topical anaesthesia had been achieved. Cellulitis was observed in four of the patients and full-thickness necrosis requiring formal debridement was observed in three patients.

To address the complications, the authors modified their technique by injecting a mixture of 10 ml 1 % methylene blue, 5 ml normal saline, 7.5 ml of 0.25 % Marcaine with 1:200,000 epinephrine and 7.5 ml of 0.5 % Xylocaine under intravenous sedation. There were no further incidences of cellulitis or skin necrosis [22].

The authors observed that loss of pin-prick sensation in the perianal area was predominant amongst the treated patients. A punch biopsy of the perianal skin at 7 years of follow-up demonstrated normal nerve axons but no sensory nerve endings on electron microscopy. Toxicity of methylene blue to nerve endings has been hypothesised as the therapeutic mode of action.

Farouk and Lee report a small series of six consecutive patients who underwent injection of methylene blue [23]. A solution of 10 ml of methylene blue (1 %) was mixed with 7.5 ml Marcaine (0.25 %) with adrenaline (1:200,000) and 0.5 % Marcaine plus 5 ml 0.9 % saline solution. This mixture was injected intradermally under general anaesthesia with prophylactic antibiotic cover (cefuroxime, 750 mg, and metronidazole, 500 mg).

Five of the six patients experienced a substantial reduction in symptoms after the injection. Patients remained under long-term follow-up and each received subsequent injections up to 5 years after initial treatment.

All patients reported numbness in the treated skin following the procedure which was tolerable.

Botterill and Sagar report a series of 25 patients with intractable pruritus ani [15]. Most (23/25) of these patients had undergone previous procedures for anorectal pathology believed to be contributing to their pruritus. The authors used a mixture of 15 ml 1 % lidocaine, 5 ml 1 % methylene blue and 100 mg hydrocortisone which was injected intradermally. After a single injection, 16 patients had relief of symptoms.

Eight of the remaining 9 patients underwent repeat injection, and 6 of these patients then achieved relief of symptoms. The overall success was 88 %. Early in the study, the authors attempted to inject under intravenous sedation only. This was abandoned in preference of general anaesthesia after 2 patients found the discomfort of injection intolerable.

The authors make an interesting technical point that may explain the mode of action of the treatment. When they observed the patients who responded to the treatment at week 2 and week 6 follow-up, the tattooing of the skin had persisted to greater than 6 weeks duration. Amongst the non-responders who had initial relief, the tattoo was present at 2 weeks but had disappeared by 6 weeks. The authors' conclusion for this was that the dye was likely to have been inadvertently injected deeply, leading to its rapid absorption and reduction of half-life and subsequent length of action on sensory nerve endings.

In their discussion, the authors address the possibility that the lidocaine or steroid may account for the symptomatic relief instead of the methylene blue. The reason given for these agents' inclusion in the injected mixture was to provide short-term symptomatic relief from pain of the injection and to reduce the perianal inflammation from the chronic irritation of pruritus. The authors come to the conclusion that the methylene blue is the active ingredient in the mixture as the lidocaine and hydrocortisone have a short half-life when compared to the longevity of the symptom relief. They do acknowledge, however, that this is unproven.

The only side effect reported in this series was a single patient who developed a transient minor faecal incontinence.

Mentes et al. report a case series of 30 patients with idiopathic pruritus ani treated by anal tattooing with methylene blue. This group did not include steroid with the methylene blue injection and also injected lignocaine alone in 6 patients prior to starting the trial. These patients all had recurrence of pruritic symptoms within 3 days and went on to successful methylene blue injection subsequently. In their series, 24 patients were symptom-free at 1 month; 5 were partial responders, 4 of whom achieved total relief with a subsequent treatment; and 1 patient did not respond at all. At 12-month follow-up, 76.7 % of patients remained symptom-free. five patients have been followed so far to 2 years and none of them have reported recurrence [14].

Sutherland et al. report the largest series of patients to undergo anal tattooing to date [16].

All patients that were referred to their unit underwent a trial of conservative management. If this failed, they were extensively worked up for secondary causes of pruritus including colonoscopy and anal mapping for underlying anorectal disorder. None of the anorectal investigations revealed pathology.

Forty-nine patients were subsequently identified with pruritus ani and underwent anal tattooing. They report that 57 % of their patients had resolution of symptoms with a total of 96 % of patients reporting significant improvement. Four of the partial responders underwent a further treatment and were rendered asymptomatic.

This group used 10 ml 1 % methylene blue mixed with 20 ml 0.5 % Marcaine with 1:200,000 epinephrine and 1 ml methylprednisolone (40 mg in 1 ml) as the initial treatment.

Sutherland reports side effects in seven patients who complained of transient faecal incontinence. This troubling symptom had resolved by 6 weeks in all patients. Two patients in their study complained that the loss of perianal skin sensation was troubling to them, and they subsequently emphasised this unavoidable (perhaps therapeutic) side effect in their consent process. This group have yet to report long-term follow-up data.

On a technical point, this group took the step of marking the symptomatic area preoperatively and ensuring that this area was completely 'inked' at the end of the procedure. Instead of linear injections along skin furrows, this group injected a series of subcutaneous 'blebs' to ensure the dye ended up in the intradermal compartment.

In summary, methylene blue tattooing seems to be a safe and dramatically successful treatment for a proportion of patients with idiopathic pruritus ani. Patients should be warned of the side effects of diminished perianal sensation that can be unpredictable in recovery: transient faecal incontinence, tattooing of the perianal skin, green-blue discoloration of the urine that lasts around 3–4 days and the possible need to repeat the procedure. Although of low risk, serious side effects

include anaphylaxis, perianal sepsis, cellulitis and skin necrosis requiring skin debridement.

It is generally recommended that the procedure be carried out under intravenous sedation or general anaesthesia as it is poorly tolerated using local anaesthesia alone.

Sutherland's technique of preoperative skin marking and subdermal bleb infiltration seems to be a sensible approach and is recommended to achieve long-term tattooing which correlates with successful outcome. A combination of steroid, local anaesthesia and methylene blue of between 0.5 and 1 % concentration should be injected. It is recommended to keep the total volume injected to less than 40 ml. Skin necrosis has been observed at a higher volume of infiltrate. Prophylactic antibiotics do not seem to be required however should be guided by local policy and operator preference.

Conclusion

Pruritus ani is uncommon but can be extremely difficult to treat. Expertise from both the dermatology and colorectal departments to identify potentially underlying disease is essential to ensure that pruritus is not a secondary symptom. When idiopathic pruritus ani has been confirmed and fails to settle with hygiene measures or stool thickeners, capsaicin treatment, if tolerated, should be instigated. If this fails or is intolerable, success may be achieved with an anal tattooing procedure using methylene blue solution which can be repeated as necessary.

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