Case Report

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Generalised Cutaneous Dysesthesia Responding to Clonazepam

Eileen J McManus[1*], Peter Wright[1] and Amanda Oakley[2]

[1]Department of Dermatology, Waikato General Hospital, Hamilton, Waikato, New Zealand

[2]Department of Neurology, Waikato General Hospital, Hamilton, Waikato, New Zealand

*Corresponding author: Eileen J McManus, Department of Dermatology, Waikato General Hospital, Hamilton, Waikato, New Zealand, Tel: 021 0874-0678

eileen.mcmanus@waikatodhb.health.nz

Abstract

We describe a rare case of distressing generalized cutaneous dysaesthesia in a patient with hypertrophic lichen planus in which neurological evaluation was normal. The dysaesthesia markedly improved with clonazepam. Most existing therapies for cutaneous dysaesthesia are symptomatic, with our case supporting a role for pharmacological modulators of GABAergic neurotransmission.

Keywords: Generalised cutaneous dysaesthesia; Gabaergic neurotransmission; Neurocutaneous syndrome

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Introduction

Cutaneous dysesthesia is a rare neurocutaneous syndrome that occurs in both generalised and localised forms. Cutaneous dysaesthesia is defined as an unpleasant and abnormal sensation in the skin. We present a case of generalised cutaneous dysaesthesia associated with hypertrophic lichen planus, highlighting the diagnostic and therapeutic challenges associated with this case. We also present a review of the limited existing literature regarding cutaneous dysaesthesia. Early recognition and treatment of cutaneous dysaesthesia are important however the treatment options for cutaneous dysaesthesia remain limited. GABAergic neurotransmission may play an important role and therefore represents a potential therapeutic target002E.

Case Presentation

A 47-year-old Māori woman presented with severe generalised dysaesthesia. Her medical history included childhood tuberculosis and a 35 pack-year smoking habit.

She described her symptoms as “tingling, lightning-shock sensations with insects crawling all over the body" including the trunk, limbs, buccal, rectal and genital areas beginning 18 months earlier, with no obvious trigger. She had a temporary remission of symptoms for several months after aortic valve replacement however her symptoms gradually re-emerged. The dysaesthesia significantly impacted on her quality of life interfering with her work as a welder and preventing sleep. She noticed that alcohol significantly alleviated the dysaesthesia “by about 60%” and was soon drinking 7 units of alcohol each day compared to tramadol, which relieved her symptoms “ by about 40-50%”. On examination, she was restless, striking at normal-appearing skin on her limbs to lessen the dysaesthesia. Power, tone, reflexes, coordination, cranial nerve examination and sensation (in all modalities) were unremarkable. Investigations were non-contributory **(Table 1)**. Trials of amitriptyline (50 mg) and promethazine (25 mg) were ineffective. A diagnosis of atypical restless leg syndrome was made but a trial of ropinirole (1.5 mg TDS) proved ineffective. A diagnosis of anxiety was considered however the patient did not meet the DSM V criteria for anxiety and had no previous mental health history.

The generalised dysaesthesia was preceded by an itchy rash on her limbs and trunk, which she reported first occurred one year prior to generalised dysaesthesia. On examination, there were multiple large, excoriated, irregular, scaly papules, nodules and pla ques on her anterior chest, upper trunk, shoulders and forearms **(Figures 1A and1B)** with someareasofpost-inflammatory hypopigmentation. Biopsy of these lesions revealed hypertrophic lichen planus **(Figure 1C)**

As she reported that the dysaesthesia responded dramatically to alcohol, she was given a prescription for clonazepam 0.5 mg BD. This lead to a 60% reduction in her dysaesthesia within one week. She was able to return to work full-time and she no longer used alcohol for symptom-control. After several months she was requiring higher doses of clonazepam 1 mg TDS therefore gabapentin was introduced in an attempt to wean down the clonazepam. Currently, she is tolerating the gabapentin up-titration (300 mg TDS) and is on a reducing regime of clonazepam (1 mg BD). She continues to work full-time as a welder.

Investigation	
Bloodwork	HbA1C, CRP, B12, folate, ANA, ANCA, dsDNA, C1 esterase, C3, C4, immunoglobulins and ferritin were all within normal parameters. SS-A (Ro) antibody was weakly positive. HIV, hepatitis B, hepatitis C and CMV serology were negative.
Nerve conduction studies	Due to allodynia, only the common peroneal motor study was tolerated. The distal latency and amplitude were normal.
MRI brain	Normal thalamus and primary sensory cortices.

Table 1: Summary of diagnostic work-up. Note that full nerve conduction study was not possible due to patient intolerance.

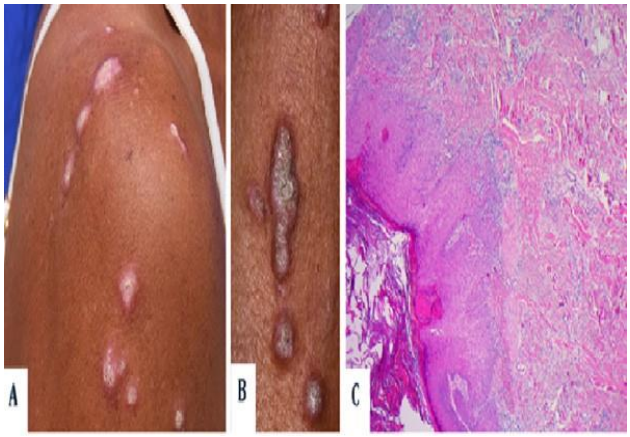

Figure 1 (A-C): Photo (A) and (B) showing scaly papules nodules and plaques of hypertrophic lichen planus. Photo (C) is photomicrograph with hematoxylin and eoslin stain (H&E) staining demonstrating hypertrophic lichen planus.

The hypertrophic lichen planus improved with acitretin 10 mg alternate days after minimal improvement with potent topical steroids and emollients. The role of clonazepam in improving her pruritus was unclear.

Discussion

Cutaneous dysaesthesia is defined as an unpleasant and abnormal sensati on unassociated with a primary skin disease and can be classified as generalised or localised. There are multiple variants of localised cutaneous dysaesthesia, which differ in location, duration, and symptom severity. There is very little literature on generalised cutaneous dysaesthesia but localized forms are well described in **Table 2** [1-9]. Localised dysaesthesia often follows nerve trauma, impingement, or irritation. This can be intracranial (in trigeminal trophic syndrome), spinal, or peripheral. Generalised cutaneous dysaesthesia is a clinical diagnosis after a detailed history and examination have excluded a primary dermatological disease. Serological tests may include testing for: Glycosylated haemoglobin (HBA1c), Complement (C3, C4), Antinuclear Antibody (ANA), Antineutrophil Cytoplasmic Antibodies (ANCA), Antibodies to Borrelia burgdorferi (found in Lyme disease), Human Immunodeficiency Virus (HIV) and viral hepatitis, C-Reactive Protein (CRP), Iron studies, Folate, Vitamin B12, Vitamin E, Heavy metal levels and/or Angiotensin-Converting Enzyme (ACE). Other tests may include Nerve conduction studies to look for demyelinating or axonal neuropathy, Cerebrospinal Fluid (CSF) analysis for oligoclonal bands if demyelination is suspected and Magnetic Resonance Imaging (MRI) of the brain and cervical spine if demyelination or ischaemia is suspected. The differential diagnosis of cutaneous dysaesthesia should be broadened if the skin is normal or abnormal (eg, lichenification might be due to eczema, nasal ulceration might be due to skin cancer). Somatisation is sometimes implicated with cutaneous sensory disorders such as compulsive skin picking [10].

Generalised cutaneous dysaesthesia can be associated with neurological diseases; including multiple sclerosis, peripheral neuropathies, and thalamic infarcts (our patient underwent extensive workup which was unremarkable). Generalised cutaneous dysaesthesia can be exacerbated by temperature change, heat, or the touch of clothing. Secondary dermatological changes associated with rubbing/scratching include excoriations, bruising, hyperpigmentation, and lichenification.

Lichen planus is a chronic inflammatory skin condition affecting the skin and mucosal surfaces. Lichen planus is a T cell-mediated autoimmune disorder, in which inflammatory cells attack an unknown protein within the skin and mucosal keratinocytes. Lichen planus may cause a small number or many lesions on the skin and mucosal surfaces. Symptoms can range from none (uncommon) to intense itch. We have found no reports of lichen planus causing or resulting from generalised dysaesthesia; however, lichen planus is known to cause severe pruritus and we speculated that the lichen planus induced additional widespread sensory symptoms. Cutaneous dysaesthesia is difficult to treat effectively with topical or oral agents in **Table 3** [1,7,11-12].

Cutaneous Dysaesthesia		Ref.
Generalised dysaesthesia	Dysaesthesia affecting most or the entire skin surface.	
Localised dysaesthesia	Usually affects the ala of the nose (V2 branch of the trigeminal nerve) with subsequent rubbing and picking causing ulceration. The trigeminal trophic syndrome can also involve the buccal mucosa, the tongue, or eye. The tip of the nose (innervated by a branch of V1) is often spared.	
Trigeminal trophic syndrome		[1]
Hand-foot syndrome	A form of cutaneous dysaesthesia affecting hands and feet during chemotherapy	[1]
Scalp dysaesthesia	Affects the skin overlying the occipitofrontalis muscle and scalp aponeurosis. This is sometimes referred to as trichodynia when associated with hair loss. Substance P, a neuropeptide, is postulated to play a key role in trichodynia by promoting mast cell degranulation and neurogenic inflammation in the hair follicle.	[1,7]
Notalgia paraesthetica	Affects the skin between the scapula and vertebrae (T2-T6). Forward flexion or extension of the arms may worsen symptoms. Notalgia paraesthetica has been linked with multiple endocrine neoplasia type 2A (MEN2A) caused by RET gene mutations.	[4,9]
Brachioradial pruritus	Affects the skin overlying the brachioradialis muscle of the forearm, on the dorsolateral aspect of the arm around the elbow. Exacerbated by sun exposure.	[5]
Meralgia paraesthetica	Affects the anterolateral thigh, the distribution of the lateral femoral cutaneous nerve. Associated with type 2 diabetes and obesity.	[6]
Glossodynia "Burning mouth syndrome"	Affects oral mucocutaneous membrane.	[8]
Genital dysaesthesia	Involves the vulva (dysaesthesia vulvodynia) or scrotum (male genital dysaesthesia and scrotodynia). accompanied by erythema.	[8]

Table 2: Summary of literature review regarding the treatment of cutaneous dysaesthesia.

Symptomatic therapy	Indication	Ref.
Capsaicin cream	All forms of cutaneous dysaesthesia	[1,7,10]
Local anaesthetic patches		
Low-dose tricyclic or another antidepressant		
Antiepileptics including gabapentin, pregabalin, and carbamazepine		
Psychotropics eg. venlafaxine and pimozide		
Topical amitriptyline 1% with ketamine 0.5%	Brachioradial pruritus	[10]
Other		
Physical barriers eg. gloves, nocturnal thermoplastic facemska, night-time arm splinting	To reduce manipulation and ulceration of tissue in trigeminal trophic syndrome	[1]
Transcutaneous electrical muscle stimulation	Notalgia paraesthetica	[10,12]
Narrow-band ultraviolet radiation		
Botulinum-A injections		
Physiotherapy		
Intralesional steroid injections	Meralgia paraesthetica	
Propranolol	Trichodynia	[11]
Cannabinoids		[7]

Table 3: Summarizing our literature review regarding the treatment of cutaneous dysaesthesia.

Conclusion

Our patient reported relief of dysaesthesia with alcohol and clonazepam, suggesting a role for GABAergic neuromodulation. This would also explain why gabapentin has relieved her symptoms, as it too modulates GABAergic pathways. The unexpected benefit of tramadol implies possible mu receptor involvement. Such patients are often misdiagnosed or mistaken for functional/psychiatric disorders. Early recognition and treatment of cutaneous dysaesthesia are important however the treatment options for cutaneous dysaesthesia remain limited.

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