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Research Article

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Sensitive Skin Syndromes and Transient Receptors Potential (TRP) Channels in Sensitive Skin

CHAN Kam Tim Michael*

Specialist in Dermatology

***Corresponding author**
CHAN Kam Tim Michael, Specialist in Dermatology, Hong Kong Academy of Medicine, Hong Kong SAR, China; E-mail: pioneerskin@ymail.com

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Abstract

Sensitive skin is a prevalent skin condition affecting both female and male worldwide without the presence of perceivable signs. The associations between sensitive skin and pre-existing skin diseases of atopy and dermatitis, dry skin, rosacea and food hypersensitivity in the gut with cognitive complications are referred to as Sensitive Skin Syndrome (SSS), making this disease more complex. Neurogenic and non-neurogenic inflammation, epidermal barrier defects, TRP ions channels interplay with the central nervous system combining with subsequent perceptive cognitive motor behaviour appears to be the main pathogenetic mechanism. Further research and studies of this intriguing condition may further enlighten us on how different systems of the body: skin, nervous system, cognition and gut integrate functionally and pathologically as a whole.

Keywords: Sensitive skin syndromes, Sensitive skin, Transient Receptors Potential (TRP) channels, Atopy, Central nervous system

Introduction

Sensitive Skin (SS) is a significant, global, complicated, clinical and public health problem with increasing prevalence [1-7]. Patient experience subjective sensory symptoms after the application of sensitive skin care products. On top of that, the subjectivity in symptomatology and the presence of transient erythema increase the difficulty in diagnosing SS. The clinical course is unclear and not fully understood scientifically [8]. SS is associated with underlying severe chronic skin diseases. The subsequent apprehension leaves both the patients and managing dermatologists feel perplexed. It is not uncommon for SS patients to demonstrate severe psychological affects during clinical consultations. SS has been shown to affect patients' Dermatology Quality of Life (DQOL) with major disease burden [1,2]. Medical legal disputes and litigations may follow after life-threatening skin diseases, both infectious and pre-cancerous are mismanaged as SS or vice versa. The dishonest and misleading labelling of the ingredients in the skin care products may also prompt investigations by health authority.

Definition

SS is a clinical condition defined by the self-reported facial presence of different sensory perception sincluding tightness, stinging, burning, tingling, pain and pruritus due to a variety of factors [1]. Stander highlighted the importance of the objective sign of erythema with tingling sensations in response to physical, chemical, physiological and hormonal factors [2]. Nonetheless, SS with its plethora of neurosensory manifestations is not only a result of contact to allergic skin care products or cosmeceutical chemicals but also many other environmental, neurosensory, hormonal, dermatological and lifestyle factors [1]. The combination of SS and pre-existing skin diseases like atopy and dermatitis, dry skin, rosacea and possibly diet sensitivity in the gut with cognitive complications are collectively referred to as Sensitive Skin Syndrome (SSS)

Historical Perspectives

Early in 1970, Frost and Kligman described a method of appraising the stinging capacity of topically applied substances to the skin. In the late 80s, Maibach coined the term "cosmetic intolerance syndrome" and its management Other author like Fisher renamed the clinical symptoms as "Status Cosmeticus"probably due to its abrupt onset sensations and undefined aetiologies [09-11]. It would be interesting to note that most of these early observations of the phenomenon of SS was originally recorded and documented in non- dermatology journals. Not until the beginning of the twentieth first century, Yospitch and Misery pioneered systemic scientific researches, investigations and studies on subjective symptoms, epidemiology and pathophysiology of SS bringing the impact of this condition to the arena of dermatology [12,13].

Epidemiology

A common skin disease with overall world prevalence reported up to 40 to 50% especially in USA and Europe [14-16]. In France, 59% women and 41% men were reported to have SS whereas 52% women and 48% men in Japan. The sensitive skin phenomena have been reported almost world wide in Brazil, Russia, China, Japan, and France in studies employing different methodologies. Reactive skin, over reactive skin, intolerant skin and irritable skin were used

synonymously as sensitive skin in the literature. Sensitive skin may look and appear as normal skin without any obvious signs. Triggering factors include environmental physical changes; skin care products used; UV radiation; skin type, air pollutions, heat, cold, wind, diet, alcohol consumption, stress, emotional burden and hormonal changes. (Figure 1) Sensitive skin showed little or no histopathological features. It is not an allergic or immunological skin disorderwhen standing alone. Reactive skin occurs more often in individuals with pre-existing skin diseases including atopic dermatitis, dry skin, rosacea, seborrheic dermatitis, psoriasis and food allergy. A female preponderance in prevalence has been reported, whereas an increasing incidence in male has been documented. Dry skin types, higher age and Dermatology Quality Life Index (DLQI) are other reported as confounding risk factors, while age, ethnicity and occupation were found to be non-significant factors. Environmental factors such as ultra-violet light and climatic change also play a role in trigging SS.

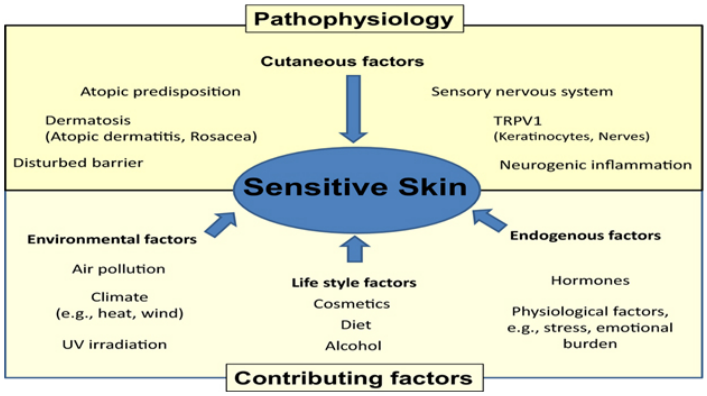


Figure 1: (Source: Reference 1)

Clinical Presentations

The most common site of presentation of SS is the face [16-19]. Up to 70% of patients reported symptoms in other areas including the scalp, genitalia, perianal, peri-vulval regions, the hands, arms and the trunk.The symptoms are subjective perceptions of skin tightness, numbness, stinging, burning, pain and pruritus. The skin may look normal though transient erythema could be observed. The neurogenic pain and distress symptoms occur usually within one hour following exposure to the triggering factors and may persist for minutes and even hours [2]. Since precise diagnostic criteria, severity assessment, aetiology and clinical management was not fully elucidated, the diagnosis of SS must include important though rare clinical differential diagnosis such as occult cutaneous, neoplastic, autoimmune and infective dermatological conditions including herpes zoster, eczema herpeticum, carcinoid syndrome, amyotrophic dermatomyositis, mastocytosis. Dermatologists caring SS patients should always be vigilant about the possibility of atypical presentation of important skin diseases including adult atopic dermatitis, dry skin, rosacea, and seborrhoea dermatitis, different types of urticaria and food allergy. Regular and careful follow-up on patients are recommended.

Pathogenesis

Epidermal Barrier dysfunction is believed to be the major contributory factor to SS. (Figure 2)

The Epidermis of our skin is the first line body defenceto changing environment. The epidermis has a very complicated multi-layer structure which is also pH sensitive [20]. The well- established model of mortar and bricks exemplified that epidermal keratinocytes consist of well hydrated corneocytes with a natural pH of 5.5 cemented by desmosomes composed of phopholipids. Inside the corneocytes, Natural Moisturizing Factors (NMF) including lactic acid, hyaluronic acid and filaggrin breakdown products and act as humectants to hold and bind water as well as to maintain the turgor of the corneocytes. The cellular wall of the corneocytes consists of filaggrin, involucrin and many newly identified proteins to provide further structural support. Individual corneocytes are cemented by desmosomes mainly made up of cholesterol, ceramides and phospholipids. A multi-dimensional, multi-layered and well-integrated structure is formed to achieve skin homeostasis, defending against environmental assaults including chemicals, physical and microbiomes attacks and promoting normal epidermal turnover. Proteases act on the Proteases Activator Receptor (PAR) and control rate of desquamation in upper most layers of epidermis, stratum corneum.

A defective stratum corneum, either acquired or innate will damage the normal physiological function of the epidermis. For instance, genetic predisposition to filaggrin deficiency will result in a thinner epidermis, less mature and poorer hydration of corneocytes with degraded corneodemosomes and increase in Trans Epidermal Water Loss (TEWL). The less acidic (increase in pH) stratum corneum will allow penetration of allergen and irritants. This explains the possible link of SS with atopy, dry skin and other pre-existing skin disease like rosacea. Most Atopic Dermatitis (AD) patients described having sensitive skin while 80% among them claimed skin conditions from being moderate to very sensitive; whereas only 64% of the control group participants without AD reportedtheir skin as being sensitive [1]. This break down of the mortar and brick structure exposed well distributed nerve endings in the epidermis to the agonists. Lack of protection and the exposure of free nerve endings enclosing the epidermal corneocytes result in sensitization of the epidermal nerves. However, unlike Atopic Dermatitis, inconclusive evidence has been found in the literature that skin microflora especially Staphylococcus aureusor its associated biofilms play a pathological role in the development of SS [21].

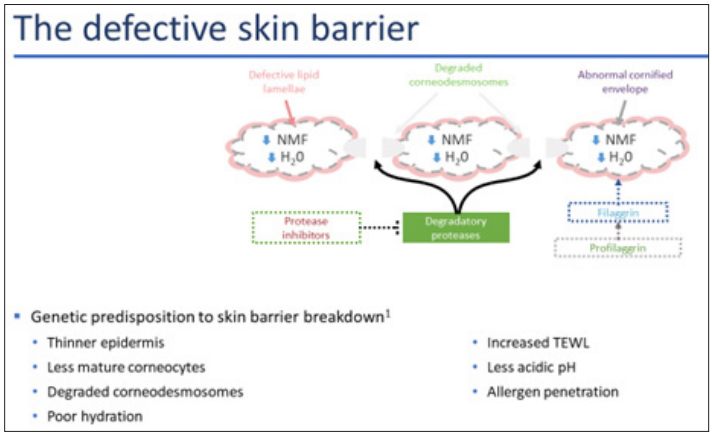


Figure 2: (Source: Reference 20)

Functional Hyperactivity of cutaneous nerves

Functional cutaneous nerve fibres such as unmyelinated C fibres mediate pain, itch and the feeling of warmth are equipped with sensory neuroreceptors such as Endothelin 1, TRP channels, Orai receptors, Serotonin receptors and PAR. TRP channels, endothelin 1; etc induce sensory sensation and itching. TRP channels are located

in nerve free endings and keratinocytes cell surface membrane and also neuronal endings in the dorsal horn of spinal cord (DRS) in the central nervous system (CNS). They are believed to play a pivotal role in the perception and pathophysiology of sensitive skin [22,23].

Role of Cutaneous Nervous System in SS

The sensory perceptions are the result of aberrant neurosensory circuitry. As mentioned above, altered sensation in patients with sensitive skin may result from insufficient protection of epidermal cutaneous nerve endings due to impaired cutaneous barrier integrity. Sensitive skin patients may have increased nerve fibre density and individual nerve fibre thickness. The phenomena of allodynia and allokinesis may be explained by new growth and proliferation of these nociceptive sensory nerves. This finding has been shown to occurin chronic AD and Prurigo nodularis (PN) patients in which nerve fibre density in lesions increased and proliferated peripherally [22,23].

TRP Channels

TRP channels can be activated by different heterogeneous physical, chemical or thermal stimuli. Which in parallel act as a trigger of sensitive skin through Ca ++ influx afferent neuronal depolarization. Studies have documented natural and chemical activators, agonists and antagonists on TRP channel receptors. For instance, TRPV 1 is activated by capsaicin, phorbol esters and heat. TRPV 3 is activated by warm temperature and camphor. TRPV 4 is activated by heat, mechanical, hyperosmotic and stress. TRPM 8 is activated by cold, menthol, wasabi and mustard and while TRPA 1 is activated by cold, wasabi, mustard, horseradish and bradykinin [23-27].

TRPV 1 is widely distributed in keratinocytes, antigen presenting cells, mast cells, and nerve free endings. Stimulation of TRPV1 releases neuropeptides and initiates neurogenic inflammation causing itch, pain and nociception [26-30]. The sensory signals are mediated through depolarization by calcium influx. TRPV can also cause cellular apoptosis and delayed epidermal recovery. TRP channels are involved in epidermal cellular homeostasis, survival and proliferation of epidermal keratinocytes, endocrine and exocrine secretions. Animal studies reported mice with TRPV 1 deficiency have significantly reduced interleukin 31 (IL31) that induces itch. Critically involved in IL-31 induced itch. This provides additional evidence that AD is linked to SS. Moreover, cutaneous immune cells are also involved in SS with activation in TRPV [31-33]. Once TRP channels are activated, it leads to the release of Substance P (SP). SP stimulate mast cells- antigen presenting cells and T cells which are all in close proximity to sensory afferent nerve endings. SP binds to receptors to induce cytokines; chemokine's and recruitment of further immune activate cells in the inflammatory cascades. TRPV expressed on T cells promotes calcium influx and CD4 positive cells activation. IL-31 produced by T cells and dendritic cells directly stimulates sensory neurons via binding IL-31 receptors found only in a subset of neurons co-expressing TRPV 1 [23-27].

Neurogenic and non-neurogenic (non-specific)inflammation

Neurogenic inflammation mediated through SP, Calcitonin G Reactive Protein (CGRP), and Vasoactive Intestinal Peptide (VIP) with vasodilatation, and mast cell degranulation. Non-neurogenic or non-specific inflammation leads to the release of IL-1, IL-8, PG E2, F2 and Tumour Necrosis Factors (TNF). Anescalating inflammatory cascade via afferent neurons activates Gastrin Releasing Peptide (GRP), Histamine 1 -4 receptors in the Dorsal Root Ganglion (DRG) of the spinal cord and Central Nervous System (CNS). Ras-Raf-MEK-ERK pathway (ERK) activation via Histamine H4 receptors in spinal neurons (Ras – Raf – MEK-ERK pathway and NMDA Na++ influx) with an imbalance of Serotonin/Dopamine/Noradrenaline in the hedonistic chronic itch pathways may also transform the acute sensory perceptions like stinging, pain and itch into chronicirritation in resistant AD and PN. The sensory signals travel to the DRG and relay messages to the thalamus in the brain. Movements with obsessive behaviour, emotional upsets, inattention, sleep disturbances and psychological cognitive malfunction may result from the subsequent imbalance of serotonin/ dopamine secretions in the S2 somatosensory area of the cerebral cortex [31-33].

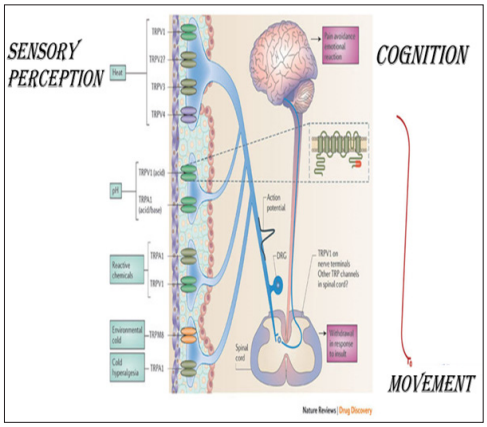


Figure 3: (Source: Nature Review/ Drug Discovery)

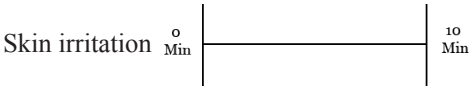
Diagnosis

In a clinical setting, a detailed clinical history is mandatory in the diagnosis of SS. Dermatologists should look for strong indicators of sensitive skin including tautness, itching and burning with the presence of certain triggering factors and transient erythema [14,16]. Objective sensory testing methods such as stinging Tests, 5% lactic acid, capsaicin test, dimethyl sufloxide test have been investigated in experimental settings with dissatisfactory correlation with SS [34]. The in-vivo electrical stimulation method has been made obsolete due to its adverse effects. At present, international consensus on the diagnosis of SS is absent. The best method to diagnose sensitive skin is utilizing self-report measures as suggested by Misery [1]. A new sensitive scale with 14 items and 10 items version would be a more preferable solution [35]. (Table 4 a,b)

DEGREE OF OVERALL SKIN IRRITATION DURING THE PAST 3 DAYS

Using a vertical line, indicates the symptoms felt during the past 3 days on the horizontal line (0 = absence of irritation, 10 = intolerable irritation)

Important: To be completed by the patient



SEVERITY OF SKIN CONDITION DURING THE PAST 3 DAYS

Please indicate the intensity of each of the following symptoms during the past 3 days.
0 = zero intensity, 10 = intolerable intensity): darken one number between 0 and 10.

Important: To be completed by the patient

Skin condition felt

Tingling	0	1	2	3	4	5	6	7	8	9	10
Burning	0	1	2	3	4	5	6	7	8	9	10
Sensations of heat	0	1	2	3	4	5	6	7	8	9	10
Tautness	0	1	2	3	4	5	6	7	8	9	10
Itching	0	1	2	3	4	5	6	7	8	9	10
Pain	0	1	2	3	4	5	6	7	8	9	10
General discomfort	0	1	2	3	4	5	6	7	8	9	10
Hot flashes	0	1	2	3	4	5	6	7	8	9	10

Visible skin conditions

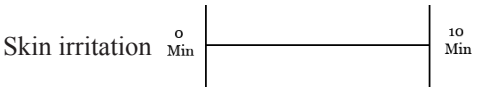
Redness	0	1	2	3	4	5	6	7	8	9	10
Scaling	0	1	2	3	4	5	6	7	8	9	10
Edema/ Swelling	0	1	2	3	4	5	6	7	8	9	10
Oozing	0	1	2	3	4	5	6	7	8	9	10
Scabs	0	1	2	3	4	5	6	7	8	9	10

Table S1: English Version of Sensitive Scale-14.

DEGREE OF OVERALL SKIN IRRITATION DURING THE PAST 3 DAYS

Using a vertical line, indicates the symptoms felt during the past 3 days on the horizontal line (0 = absence of irritation, 10 = intolerable irritation)

Important: To be completed by the patient



SEVERITY OF SKIN CONDITION DURING THE PAST 3 DAYS

Please indicate the intensity of each of the following symptoms during the past 3 days.
0 = zero intensity, 10 = intolerable intensity): darken one number between 0 and 10.

Important: To be completed by the patient

Skin condition felt

Tingling	0	1	2	3	4	5	6	7	8	9	10
Burning	0	1	2	3	4	5	6	7	8	9	10
Sensations of heat	0	1	2	3	4	5	6	7	8	9	10
Tautness	0	1	2	3	4	5	6	7	8	9	10
Itching	0	1	2	3	4	5	6	7	8	9	10
Pain	0	1	2	3	4	5	6	7	8	9	10
General discomfort	0	1	2	3	4	5	6	7	8	9	10
Hot flashes	0	1	2	3	4	5	6	7	8	9	10

Visible skin conditions

Redness	0	1	2	3	4	5	6	7	8	9	10

Table S2: English Version of Sensitive Scale-10.

Management

With the absence of confirmatory diagnosis, severity assessment, long term outcomes and possible complications of SS, the sensitive skin syndromes are still not fully understood. AD, dry skin associated dermatitis and rosacea are well associated with sensitive skin as they share similar pathogenetic mechanisms especially the epidermal barrier defects and TRP channels abnormalities. A cost-effective and standardized patient self-reported questionnaire and a suspicion on skin sensitivity history should point to the direction of SS diagnosis. Counselling, education, explanation during consultation are essential. Public health education should be reinforced to advice the public to choose appropriate skin care products for their own skin based on their level of skin sensitivity. The public especially those required to apply makes-up and cosmetics products on their jobs should be vigilant in contaminated, irritable and even toxic skin care products widely promoted in the markets and internets.

Through disentangling the relationship between the pathogenesis of sensitive skin and TRP channels and TRPV1 antagonist, it indicates that trans-4-tert-butylcyclohexanol and licochalcone are effective in treating sensitive skin [36]. Pimecrolimus down regulates TRP receptors, decrease TWEL and may increase epidermal thickness [37,38]. Low energy level laser and intense pulse light has been shown to reduce the severity of sensitive skin [39]. Intense pulse light and pulse dye laser are also known to be effective and harmless treatment modalities in managing Rosacea which may link with SS [40].

Conclusion

Sensitive skin is a prevalent skin condition. There are inadequate scientific data available to the practicing dermatologists and the general public to prevent and manage the disease. Skin barrier defects, cutaneous nervous system hypersensitivity, TRP channels and immune dysfunction together with their interaction provide a plausible pathogenesis of SS. Pharmacogenetic research on TRP ion channels receptors including TRPV1,TRPV3, TRPV4, TRPA1 and TRPM1 and imaging studies like Magnetic Resonance Imaging of the CNS including the brain and its circuitry may shed light on this complicated disease. This may also enlighten us on the close interaction between skin, brain and subjective perceptual motor behavior in SS. Dermatologists should shift from the unilateral to a more dualistic, integrative approach to skin diseases like SS and Skin Sensitivity Syndrome (SSS). Pharmacological studies and clinical trials involving TRP Ion Channels blockers and activators may provide new targeted drug therapy in managing SS and its associated syndrome as well as conditions including adult Atopic Dermatitis and Rosacea which are difficult to treat.

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