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Clinical Review on Sensitive Skin: History, Epidemiology, Pathogenesis and Management

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Abstract

Sensitive skin syndrome is a common and important clinical condition not only to the dermatologists but also to the skin care products and cosmetic manufacturing industries. The perception of distressing sensory symptoms like pain and itch are translated to the brain through abrupt neuronal depolarization sometimes in normal circumstances without any signs. Previously only regarded as an over reactive skin to cosmetics and toiletries, sensitive skin gained increasing attention as a syndrome of aberrancy of the nervous system of the skin and the epidermal keratinocytes. The following is a review on the history, epidemiology, pathogenesis and management of the condition.

Keywords: Sensitive skin syndrome; Definition; Neuropathic pruritus; Epidermal barrier dysfunction; TRP channels antagonists; Prevention

Introduction

Sensitive skin syndrome (SSS) is a complex, clinical, global and public health problem [1-7]. In the past, many has neglected its identity as a syndrome and merely regarded it as psychosomatic or allergic reaction to cosmetics [8]. Epidemiological data worldwide over the years has confirmed its real existence and significance [9-13]. Patients suffered from SSS presented mostly with subjective sensory symptoms sometimes with psychological consequences [14]. As clinical signs are transient and few, diagnosing the condition in a busy clinical setting is challenging. It negatively affects patient's Dermatology Life Quality Index (DLQI) and Quality of Life (QOL). SSS with its complications impacted a major public health burden to the society and health care system. Extensive availability of irritant skin care products in the markets with its misuse together with other factors like pollutions, climatic and life style changes; an escalating prevalence may be expected. The subsequent adverse reactions and patient dissatisfaction with management may prompt medical litigations and legal disputes.

Definition

Misery clarified SSS as a syndrome characterized by self- reported facial presence of different sensory perceptions including tightness, stinging, burning, tingling, pain and pruritus to a variety of factors [1]. The subjectivity of this condition is well expressed in this definition. Stander added the occasional objective sign of erythema [2]. Farage and Maibach thought that the skin in SS is prone to the subjective perception of irritation after using cosmetics and toiletries only [4]. In 2017, a special interest group of the International Forum for the Study of Itch (IFSI) defined SSS as "A syndrome defined by the occurrence of unpleasant sensations (stinging, burning, pain, pruritus, and tingling sensations) in response to stimuli that normally should not provoke such sensations. These unpleasant sensations cannot be explained by lesions attributable to any skin disease. The skin can appear normal or be accompanied by erythema. Sensitive skin can affect all body locations, especially the face" [15].

Historical Perspectives

Table 1 illustrated the historical description of SSS as cited in the literature [16-19]. Interestingly, in the early years, SSS had been described as an intolerant reaction to cosmetics, chemicals and toiletries applied to the skin particularly over the face. As the manifestations and pathogenesis of the syndrome was obscure, various terminologies had been used. Reactive skin, overreactive skin, intolerant skin and irritable skin were used synonymously as SSS in the literatures.

Years	Authors	Title	Journal
1970	Frosch and Kligman A	The method of appraising the stinging capacity of topically applied substances	J Soc Cosmet Chem. 1977; 28: 197-209
1987	Maibach HI	The cosmetic intolerance syndrome.	Ear Nose Throat. 1987; 66: 29-33
1988		Management of cosmetic intolerance syndrome.	Clin Dermatol. 1988; 6: 102-7
1990	Fisher AA	"Status Cosmeticus" A cosmetic intolerance syndrome.	Cutis. 1990; 40: 109-10
1999	Yosipovitch G	Evaluating subjective irritation and sensitive skin.	Cosmet Toiletries. 1999; 114-42
2009	Misery L	Sensitive skin in Europe.	J Eur Acad Dermatol Venereol. 2009; 23: 376-81
2011		Sensitive skin in American population: Prevalence, clinical data and role of the dermatologist.	Int J Dermatol. 2011; 50: 961-7

Table 1: Historical description of SSS as cited in the literature

This inevitably made scientific and epidemiological study of SSS difficult and impossible. Advances in neurosciences and collaborated worldwide data collection provide medical evidences SSS is a common, prevalent and significant skin syndrome occurred in all ethnic groups [1,2,15].

Epidemiology

SSS is a common skin syndrome with overall world prevalence reported up to 40% to 50% especially in USA and Europe [10,11]. An increased prevalence in the USA has been assessed by Farage [12]. There is a female preponderance in prevalence. Female gender is more often affected but can also occur in man. Recent studies reported male has an increasing incidence. In France; 59% women and 41% men and in Japan 52% women and 48% men were reported to have experience of the sensitive skin syndrome [1]. In subsequent study; although different methodologies employed involving different skin prototype, weather, lifestyle, culture; the sensitive skin phenomena were reported almost worldwide: Brazil, Russia, United Kingdom, China, United States, Japan and France [9-13]. Sensitive skin very often appears as normal skin without any objective signs.

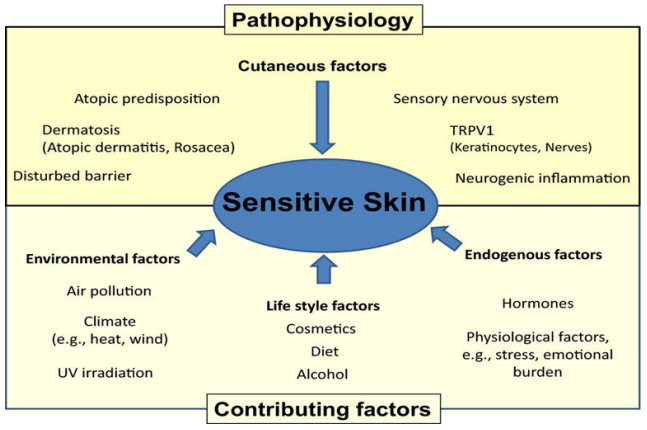


Figure 1: Transient Receptors Proteins (TRP) channels aberrancy are main suspected pathogenetic factors.

The subjective sensations of tightness, stinging, burning, tingling, pain and pruritus may occur paroxysmal or exacerbated by triggering factors include environmental physical changes; skin care products used; ultra-violet radiation; skin type, air pollutions, heat, cold, wind, diet, alcohol consumption, stress, emotional burden and hormonal changes. Dry skin types, higher age and DLQI are other confounding risk factors. Prevalence is reported to be increased in summer but there is no difference found among different age group, ethnicity and occupation according to study [20]. SSS is not an allergic and immunological skin syndrome and there is little to no histopathological features apart from very mild non-specific inflammatory cell infiltrate in the dermis. Thus, a detailed medical history and a standardized questionnaire in the evaluation and monitoring the subjective sensory perceptive discomforts and transient redness of SSS is essential and mandatory. An epidermal skin barrier impairment; peripheral and central nervous system signalling defects and Transient Receptors Proteins (TRP) channels aberrancy are main suspected pathogenetic factors (Figure 1).

Clinical Presentations

The symptoms are subjective perceptions of skin tightness, numbness, stinging, burning, pain and pruritus under normal circumstance (see definition) occur suddenly or secondary to known triggering factors (Figure 1). The neurogenic nociceptive, pruritogenic distress symptoms usually occur within one hour following exposure to the triggering factors and may persist for minutes and even hours [2]. The skin may look normal with transient erythema. Most notable location of sensitive skin is the face but can happen in any parts of the skin of the body includes hands, scalp, arms, genital areas, perianal region, scrotum and the trunk. 70% reported extra facial presentations; hands (58%), scalp (36%), feet (34%), neck (27%), torso (23%), back (21%) [1,21,22]. Currently, the diagnostic criteria, severity assessment, etiology, therapy and clinical management are unresolved. While facing suspicious presentations of SSS, important albeit rare occult neoplastic, autoimmune, allergic drug and infective dermatological conditions must be excluded. Regular and careful follow up of patients are recommended. Important skin conditions that may mistakably diagnosed as SSS are herpes zoster ophthalmicus; eczema herpeticum; trigeminal and various forms of neuraglia, carcinoid syndrome with facial flushing, mastocytosis and amyotrophic dermatomyositis.

Pathogenesis

Abnormal sensory perceptions, neuronal hypersensitivity, epidermal barrier defects, Transient Receptor Potential (TRP) ions channels, neurogenic and non-neurogenic inflammation interplay with the central nervous system with subsequent perceptive cognitive behaviour appears to be the main pathogenetic mechanism behind SSS.

Role of cutaneous nervous system in SSS

There is suggestion that the sensory perceptions in SSS are due to an aberrant neurosensory circuitry [23]. Altered sensation in patients with SSS may result from an insufficient protection of epidermal cutaneous nerve endings due to impaired cutaneous barrier integrity. Intraepidermal nerve fibre density, especially that of peptidergic C-fibres, was lower in sensitive skin. These fibres are involved in pain, itching and temperature perception and their degeneration may promote allodynia and allokinesis. These results suggest that the pathophysiology of skin sensitivity may resemble neuropathic pruritus within the domain of small fibre neuropathy [24].

Functional hyperactivity of cutaneous nerves

Functional cutaneous nerve fibres such as unmyelinated polymodal C fibres mediating pain, itch and warmth are equipped with sensory neuroreceptors such as endothelin, TRP channels, orai receptors and serotonin receptors. TRP channels, endothelin; etc induce sensory sensation and itch. TRP channels are located in nerve free endings and keratinocytes surface membrane and also central nervous system. TRP channels can be activated by different heterogeneous physical, chemical or thermal stimuli, which in parallel act as trigger of SSS through Ca^{++} influx afferent neuronal depolarization [25,26]. For instance, it is well established that TRPV 1 is activated by capsaicin, phorbol esters and heat; TRPV 3 by warm temperature and camphor; TRPV 4 by heat, mechanical, hyperosmotic gradients and stress; TRPM 8 by cold, menthol, wasabi and mustard; TRPA 1 by cold, wasabi, mustard, horseradish and bradykinin. Ingredients in cosmetics and skin care products which act as additives, preservatives may contain TRP channels agonists, activators and antagonists (Table 2).

TRP Channels	
Compounds interact with TRP Channels	
TRPV1	Capsaicin (1)
	Resiniferatoxin (1)
	Capsazeoine (3)
	Ruthenium red (3)
	UV light (1)
	Thermal stimuli (>43C) (1)
	Acidic condition (pH<5.9) (1)
	Endogenous bradykinin (1)
	Nerve growth factor (1)
	Endogenous cannabinoid lipids like anandamide(1)
	Aracbidonvly serotonin (3)
	Arvanil (1)
	2 Aminoethyl diphenylborinate (2-APB) (1)
	Metabolites of Arachnidonic acids (1)
	ATP (1)
	Histamine (1)
	Trans-tert-butyl cyclohexanol (TTBC) (ID 1609) (2)
	Lactic acid (1)
	Sodium Lauryl Sulphate (1)
	Phenoxyethanol (1)
	DMSO (1) Menthol (1)
	Clotrimazole (1) Retinoids (1) Tacrolimus (1)
Compounds interact with TRP Channels	
TRPV3	Nitric oxide (1)
	Moderate Thermal heating (32C) (1)
	Plant derived monoterpenoids: menthol, camphor, Carveol, thymol, eugenol, citral (1)
	Incensole acetate (1)
	Plant cannabinoids like tetrahydrocannabinol (1)
	2-APB (1) Unsaturated free fatty acids (1)
	Chloroquine (1)
	Clotrimazole (1)
	Hypoxia (1)
	Farnesyl Pyrophospate (FPP) in cholesterol synthesis (1)
Note: Activators=1, Agonist=2 and Antagonist=3	

Table 2: TRP channels agonists, activators and antagonists.

Examples of these irritants which act through TRPV 1 activations are sodium lauryl sulphate; lactic acid; formaldehyde-releasing preservatives alternatives like phenoxyethanol, flavour and fragrance agents like trans-4-tert-butylcyclohexan-1-ol (TTBC). TRP channels are believed to play a pivotal role in the perception and pathophysiology of SSS [27].

Epidermal barrier dysfunction

The stratum corneum is the principal barrier to irritants and allergens and is involved in the regulation of trans epidermal water loss (TEWL) [28]. The defective epidermal barrier maybe secondary to the action of irritants, proteases and protease activated receptors (PAR). The abnormal epidermis clinically presented as dry skin increase TEWL from the inner body to the outside environment while; in the reverse; allows penetration and invasions of allergens, irritants and pathogens from the outside to the inner body activating its immune-neurological defence pathways. As mentioned, the broken epidermis exposed the free nerve endings between the epidermal keratinocytes which are well equipped with the sensory receptors like TRP channels and others. Cytokines and immune mediators like prostaglandins may be secreted and resulted in neurogenic inflammation through the release of histamine from mast cells [29]. Substance P (SP) is also known to be involved as in other inflammatory diseases both in the skin and the spinal cord. Interestingly, sensitive skin has been linked with atopy. Dry is more frequent in SSS but sensitive skin is not dry in the majority of cases [30]. Patients with sensitive skin may have a defective epidermal barrier characterised by a thinner epidermis, less mature coenocytes, enhanced degradation of corneodesmosomes (due to decreased expression of protease inhibitors, increased expression of proteases and elevated skin pH), defective lipid lamellae, poor hydration and reduced levels of natural moisturising factor. Hence, SSS may be associated with an epidermal barrier dysfunction with subclinical inflammation. Hillion in his study reveals there is no dysbiosis of aerobic cultivable bacteria associated with SSS [31].

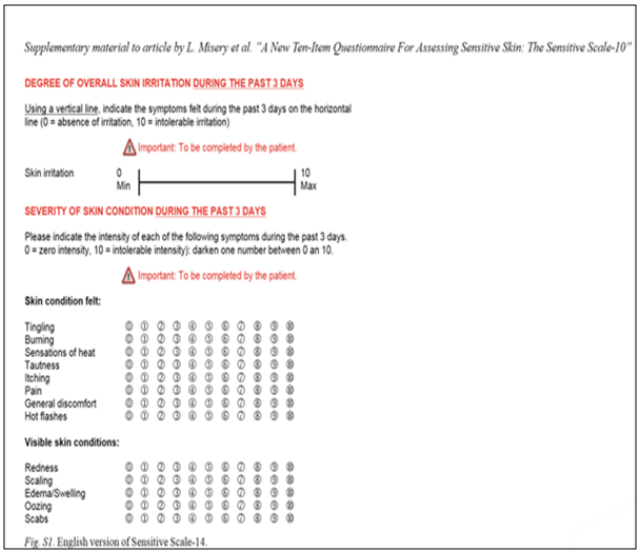
Neurogenic and non-neurogenic (non-specific) inflammation

Neurogenic inflammation mediated through SP, Calcitonin G Reactive Protein (CGRP), 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). An escalating 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). 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 [32-34].

Diagnosis

A detailed and systematic clinical medical history is crucial in the diagnosis, evaluation, management and follows up of SSS [30]. A 14 items and 10 items self- reporting sensitive scale questionnaires has been developed and validated in evaluation and monitoring of SSS [35]. (Figure 2) Strong indicators of sensitive skin is tautness, itching and burning under certain triggering factors and transient erythema. Objective tests and investigations like sensory testing methods, stinging tests, 5% lactic acid tests, capsaicin test, dimethylsufloxide test

are not diagnostic and possess technical limitations and may not be acceptable to the patients. [1,35] Previously, an electrical method to simulate the sensory perception has been abandoned and become obsolete. there is no international consensus or preferred method recommended. There is a pressing need to assess the subjective symptoms of the patients of SSS to prevent possible complications and co-morbidities. The best method to diagnose SSS is still utilizing a patient self-reported scale.



Supplementary material to article by L. Misery et al. "A New Ten-Item Questionnaire For Assessing Sensitive Skin: The Sensitive Scale-10"

DEGREE OF OVERALL SKIN IRRITATION DURING THE PAST 3 DAYS

Using a vertical line, indicate 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.

Skin irritation 0 Min — 10 Max

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 an 10.

Important: To be completed by the patient.

Skin condition felt:

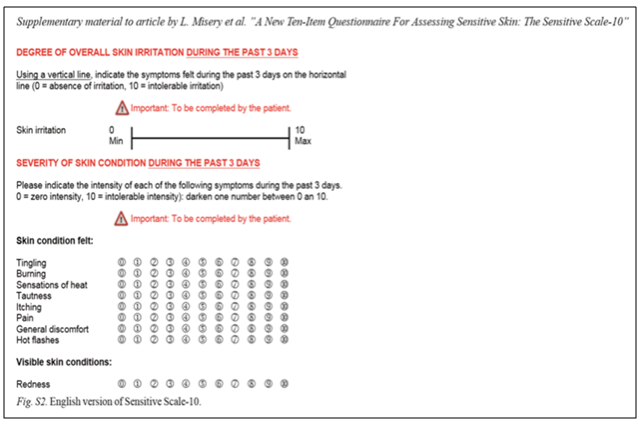
Tingling
Burning
Sensations of heat
Tautness
Itching
Pain
General discomfort
Hot flashes

Visible skin conditions:

Redness
Scaling
Edema/Swelling
Oozing
Scabs

Fig. S1. English version of Sensitive Scale-14.

Figure 2A: A fourteen items questionnaire version for assessing sensitive skin.



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Important: To be completed by the patient.

Skin condition felt:

Tingling
Burning
Sensations of heat
Tautness
Itching
Pain
General discomfort
Hot flashes

Visible skin conditions:

Redness

Fig. S2. English version of Sensitive Scale-10.

Figure 2B: A ten items questionnaire version for assessing sensitive skin.

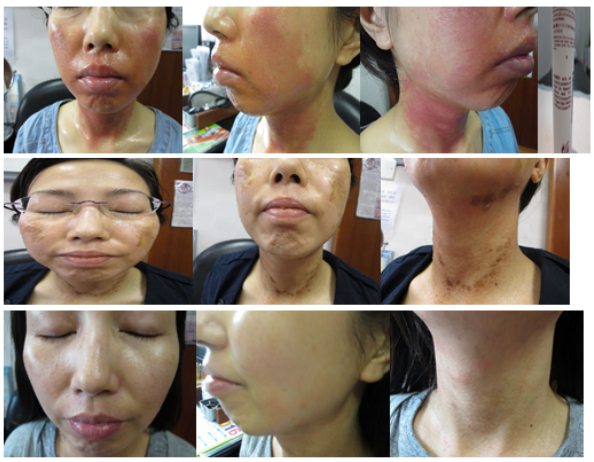

Figure 3: Sensitive skin-A Real Concern. Day 1: Patient with a history of sensitive skin presented with severely inflamed burning tightening erythematous skin eruption over site of application of irritating skin care products, Day 4: Gradual improvement of skin condition after stopping the suspicious skin care products with liberal use of non-irritant moisturizers without topical or systemic steroids, Day 7: Complete recovery after continuous moisturization.

Management and treatment

As confirmatory diagnosis, severity assessment, long term outcomes and possible complications of SSS are still not fully understood, management of SSS is challenging and difficult. SSS and its associated complications like irritants dermatitis is a real clinical concern.

Figure 3 showed a patient presented with a long history of SSS symptoms involving the face and hand developed acute irritant burning, tightening and painful lower face and neck dermatitis after applying skin care products containing irritant preservatives and additives supplied by her own mother at home.

She recovered after stopping the causative skin care products, liberal moisturizers, humectants and occlusive emollients and total avoidance of systemic and topical steroids. Her gradual recovery was shown as evident by the restoration of the healthy epidermal barrier. Counselling, careful explanation and total abstinence of inappropriate use of unsuitable or even dangerous skin care products are essential. Public education particularly on the vigilant selection and application of non-irritative, non-sensitive and safe skin care products like cleansers and moisturizers are important management [36]. Recently through understanding the possible pathogenesis of sensitive skin with TRP channels, TRPV1 antagonists like 4-t-butylcyclohexanol and licochalcone have been proposed in small scale study to be effective in treating SS [37]. Non-steroidal, anti-inflammatory cream; pimecrolimus; down regulate TRP receptors, decrease TWEL and increase epidermal thickness may be used satisfactory but the patients must be informed about the initial burning, stinging discomfort of the compound. The use of drugs is not validated and may only reflect doctor's preference in using these drugs and have not been properly investigated in clinical trials [38,39]. Low level laser and low-level energy device like Intense Pulse Light has been shown to reduce severity of sensitive skin in one study [40]. Two clinical trials were performed in France and Thailand, a new topical combination

cosmetic product applied in patients with sensitive skin, a preventive soothing effect; an immediate soothing effect and a soothing effect on erythema were observed [41]. Last, not least, ingestion of probiotics including Lactobacillus paracasei NCC2461 (ST11) strain has been shown to reduce the occurrence of SSS in another study; though not verified; showed the complex interaction of the SSS with skin food allergy and hypersensitivity of food in the gastro-intestinal tract [42].

Conclusion

With the advance of neuroscience and collaborative epidemiological studies and researches, the puzzling condition of SSS begin to be unveiled. Defective epidermal skin barrier, neuronal receptors sensitization, neuropathic pruritus secondary to small fibre neuropathy, neurogenic inflammation interacted with endogenous and exogenous triggering factors resulted the distressing cognitive perception of SSS. Local consumer councils, health departments, managing doctors and skin care manufacturing industries are all stakeholders and have a social responsibility in explaining, informing and educating the public of all age groups in understanding and preventing exacerbation of SSS. Dermatologists should take the lead and act as gate keeper and participate in an active role in managing and preventing this global public health problem.

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