A Systematic Review of Sensitive Skin Syndrome with its Proposed Pathogenetic Mechanism of Small Fiber Neuropathy

Kam Tim Michael Chan*
Hong Kong Academy of Medicine, Hong Kong SAR, China

Abstract

Sensitive skin syndrome is a common skin condition present predominantly with subjective neurological symptoms. Its etiology and pathogenesis are still unclear. Its management is difficult. The absence of a confirmatory diagnostic test made sensitive skin poses diagnostic and therapeutic challenges to clinicians especially in primary health care setting. Small fiber neuropathy has been proposed as one of the pathogenetic mechanism. A Pubmed systematic literature search was performed to reveal scientific evidences on sensitive skin syndrome pathogenesis and its relation to small fiber neuropathy. The review aims to illustrate evidence base data on the pathological mechanisms of sensitive skin syndrome, to clarify unproven claims, to enable front line health care service provider’s scientific knowledge in counselling, education, prevention, and management of this complicated condition.

Keywords: Sensitive skin syndrome; Review on pathogenesis; Adhesion focus; Genomics; Intraepidermal nerve fiber; Nerve growth factors

Introduction

Sensitive skin syndrome (SSS) is a complex, global, clinical and public health problem affecting all ethnic groups with increasing worldwide prevalence [1-7]. Patients experience subjective neuro sensory symptoms of skin tightening, burning, tingling, numbness, pain and itch under conditions like wind, heat, sunlight, food, application of cosmetics, shampoo and physiological activity like sleep that are normal or trivial to the unaffected [8-11]. The International Forum of Study of Itch (IFSI) defined SSS as a syndrome with the occurrence of unpleasant sensations (stinging, burning, pain, pruritus, and tingling sensations) in response to stimuli that normally should not provoke such sensations [12]. These unpleasant sensations cannot be explained by lesions attributable to any skin disease. The skin can appear normal or be accompanied by erythema or swelling. The transient erythema, swelling and inflammatory signs make SSS clinical diagnosis and management difficult. As reported in the literature, known pathogenesis of SSS include epidermal barrier dysfunction, trans epidermal water loss (TEWL), hypersensitivity and aberrancy of the cutaneous nervous system including Transient Receptor Potential Vanilloid (TRPV) channelopathy, neurogenic and non-neurogenic (non-specific) inflammation and recently small fiber neuropathy is proposed [11,13-26]. The pathogenesis of SSS is not completely elucidated and understood, the clinical course and prognosis remained unclear and speculative.

In view of this, a systematic literature search regarding the possible pathogenesis on SSS particularly on the recently suggested association of peripheral neuropathy and SSS was performed. The underlying objectives are to provide scientific based evidences on the pathogenesis of SSS especially regarding neuropathy; clarification on misconceptions SSS patients may have on this complicated syndrome. The data may facilitate and promote patient counseling, education, prevention and management including treatment especially in a primary and specialist clinic setting.

Methodology

There are no previous studies reporting and investigating the direct relationship between peripheral neuropathy and SSS. However, the link between sensitive skin and disrupted skin barrier is well reported. Therefore, in the case of sensitive skin, it is highly possible that increased TEWL and decreased epidermal barrier integrity may facilitate the penetration of irritant or allergen into the skin. This would eventually induce more stress in the skin and lead to alternation in epidermal nerve innervation and affect the perceived dysfunctional sensation. Therefore, the following keywords are used for this literature search: “sensitive skin”, “intraepidermal nerve fiber”, “epidermal nerve innervation”, “trans epidermal water loss (TEWL)”, “tight junction” and “focal adhesion”. The online published articles are searched on the PubMed database based on above keywords. A unique identifier is assigned to an online journal article. The PMID is a unique identifier used to locate articles online as most publishers assign these to their online content. The followings are the literatures (listed with their PMID) with a brief summary or the reason of why they are related to this topic.

Result

A total of eleven Pubmed indexed articles with their PMID were retrieved, their PMID and author summary and the reasons why they are related to the topic of neuropathy and SSS are listed in Table 1. There were no PMID results found based on direct key word search based on peripheral neuropathy and sensitive skin syndromes.

A more detailed descriptions on these studies objectives, methodology, findings, limitations and authors conclusions were appended in Annex 1.

Discussion

The above systematic review is to unambiguously reveal evidenced based, documented scientific and molecular features involved in the pathogenesis of a complex disease SSS. Besides useful in further our scientific understanding, data extracted would be of practical significance in enhancing effective deliverance of education, counselling, explanation and clarification of some unsubstantiated
proposals which may still lack scientific proofs to patients in clinical setting. Service providers, the cosmeceuticals industries; alike patients; should be informed and aware of these already existed published findings and the implications.

Focal adhesion of keratinocytes in stratum corneum (SC) of skin epidermis, patient's genotypes, intraepidermal nerve fiber, nerve growth factors, matrix metalloproteinasises involved inflammation and TEWL were the key underlying features revealed by the systematic literature search on pathogenesis of SSS but not neuropathy. Our study failed to reveal any published literature on any study directly investigating relationship between SSS and small fiber peripheral neuropathy.

Focal adhesion, genomics, TEWL

Focal adhesions; also referred as cell-matrix adhesions in cell biology; are sub-cellular structures made up of large sized molecular proteins. These proteins propagate biochemical signals between extracellular matrix (ECM) and connecting cells [26,27]. Focal adhesions mediate, regulate and orchestrate signaling cells to cells events in response to ECM adhesion [26,27]. An example is the epidermal binding protein integrin which enable the anchoring of keratinocytes to the basement membrane of epidermis [27] PMID 24036537 provided a good review of the important roles of focal adhesions; multi protein assemblies traverse the plasma membranes that link the cellular cytoskeleton to surrounding extracellular matrix. It plays a critical role in adhesion, cell signaling and regulatory functions of skin homeostasis and tissue response to injury [27]. Most integrins subunits are expressed in skins. Other examples of these proteins are spectraplakin protein complex like Actin-Crosslinking Factor 7 (ACF7); claudin protein complex like Claudin5 (CLDN5) and zonula occludens [18,26].

A great number of these macro-protein structures are discovered and their expression through transcription and translation are tightly controlled by genes. The study PMID 29383128 suggested the gene LNC_000265 may play a role in the epidermal barrier structure of tight junctions by regulating the expressions of CLDN5 in SSS through wide genome and proteomics study [18], LNC_000265 and CLDN5 of the claudins gene family were expressed at low levels in skin tissues of subjects with SSS compared with normal skin (p<0.05) [18]. The study PMID 27216888 suggested that another focal adhesion macro-molecule F actin; through phosphorylation of ACF7 binding; played a crucial role in focal adhesion dynamics and epidermal cellular migration in vitro and in vivo [26]. Our literatures review suggested evidences that epidermal barrier defects secondary to focal adhesions aberrancy controlled by genomics in individuals suffered from sensitive skin is a major role in the pathogenesis of SSS. This may have significant clinical impact in elucidating diagnosis screening test and management of SSS.

Abnormal skin thickness and dry skin type are common SSS clinical presentations [1,3,11]. Cell migration or turnover of the epidermis is an integrated genetically controlled process through focal adhesions integrating the activities of cytoskeleton and ECM [18,26,27]. Focal adhesions may also provide molecular basis and scientific explanation of these clinical associations as the signalling and regulation of epidermal turnover, differentiation and normalization are genetically determined and aberrant in SSS patients. Moreover, it is possible that increased TEWL and the aforesaid decreased in epidermal integrity may facilitate penetration of allergens and irritants into the skin. TEWL is scientifically investigated in PMID 21251084, 17643268 and 28262741 are essential features seen in SSS. However, one needed to be cautious not all SSS patient suffered from dry skin [23-25]. Hence; albeit genotype and genetic mutations may play a role in SSS; other molecular factors as suggested by PMID 17643268 like nerve growth factors stressed skin sensory nerve innervations is primarily or sequentially involved in the pathogenesis of SSS leading to an increasing density of intraepidermal nerve fiber [23].

Nerve growth factors, intraepidermal nerve fiber, matrix metalloproteinases and inflammation

Nerve growth factor is a neuropeptide that is expressed by keratinocytes, dermal cellular components like the mast cells, fibroblasts, eosinophils, CD4+ T-lymphocytes, neurons in the nervous system including the Dorsal root ganglion (DRG) and Central nervous system (CNS) and interestingly, the beta cells of the pancreas. Its biological functions are vast consisting of neuron projection, elongation and differentiation; negative neuron apoptosis, peripheral nervous system development, positive regulation of collateral sprouting and modulation of chemical synaptic transmissions via various neurotransmitters. Nerve growth factor is also actively involved in body immune function like inflammation in nociception and pruritus [22]. Nerve growth factor stimulate adrenocorticotrophic hormone (ACTH) in the hypothalamic-pituitary-adrenal axis which in turn act on the adrenal cortex to secret the stress hormone cortisol. In a repetitive recursive model, ACTH positively feedback the release of nerve growth

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<th>PMID</th>
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<tr>
<td>29383128</td>
<td>A genome-wide study which profiled the long non-coding RNA and mRNA in human subjects with sensitive skin, suggested the involvement of focal adhesion and tight junction in the pathogenesis of sensitive skin [18].</td>
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<td>29370274</td>
<td>Visualizing the morphology of small nerve fibers in human skin biopsy, this study suggested that women have higher density of intraepidermal nerve fiber than men regardless of the age group [19].</td>
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<td>26805416</td>
<td>Part of this review summarized that sensitive skin is more frequently observed in women [1]. These two literatures; 29370274 and 26805416; together proposed a possibility that increased density of intraepidermal nerve fiber is related with the incidence of sensitive skin.</td>
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<td>19443185</td>
<td>Atopic dermatitis patients have higher density of intraepidermal nerve fiber and expression level of nerve growth factors in skin [20].</td>
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<tr>
<td>24628070</td>
<td>Part of this review summarized the distribution of nerve fiber in skin of atopic dermatitis patients [21].</td>
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<td>17635286</td>
<td>Nerve growth factor-stressed skin increased sensory nerve innervation [22].</td>
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<td>17643268</td>
<td>In acne-treateed mice, increased TEWL, expression of nerve growth factors in skin and epidermal growth were observed [23].</td>
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<tr>
<td>21251084</td>
<td>Mathematical models suggested the increased TEWL in volunteers with sensitive skin [24].</td>
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<tr>
<td>28262741</td>
<td>A 3D self-organized cell model demonstrated how TEWL induced epidermal change and barrier function [25].</td>
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<tr>
<td>27216888</td>
<td>This study suggested the involvement of focal adhesion in epidermal migration, i.e. the turnover of epidermal cells. Together with the genome-wide study (29383128), these studies raised a possibility that epidermal thickness is also related with sensitive skin [26].</td>
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<td>24036537</td>
<td>A review summarized the role of focal adhesion in skin [27].</td>
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Table 1: A total of eleven PubMed indexed articles with their PMID were retrieved, their PMID and author summary and the reasons why they are related to the topic of neuropathy and SSS.
factor in the cerebral cortex and hypothalamus [22]. Nerve growth factor modulates neurogenesis, neural plasticity and axonal outgrowth but the reverse may be possible if excessive, uncontrolled and prolonged secretions of cortisol may inhibit nerve growth factor expression in the brain. The study carried out in PMID 17639286 suggested high stress perception results in an intense cross talk between the skin and skin innervating DRG increases the likelihood of nerve growth factor-dependent neurogenic skin inflammation by enhancing sensory skin innervation [22].

PMID 24628070 provide a comprehensive review of nerve growth factor and Sema3A produced by keratinocytes and fibroblasts in sensitive skin modulate nerve growth into ECM through production of neuronal matrix metalloproteinase. Nerve growth factor promotes matrix metalloproteinase-2 production in sensory nerve fibers and activates pro-matrix metalloproteinase-2 on the growth cone [21]. Activated matrix metalloproteinase-2 on the growth cone may contribute the penetration of nerve fibers into the basement membrane. In the dermis nerve growth factor also promotes matrix metalloproteinase-8 production in sensory nerve fibers secreted by nerve fibers [21]. Activated matrix metalloproteinase-8 may be involved in sensory nerve growth within the interstitial collagen matrix, basement membrane, epidermis and dermis. Sema3A have the opposite effects [21]. Thus, the evidence suggested that nerve growth factor act as a signal protein pivotally involved in SSS especially in promoting intraepidermal nerve fiber in the epidermis and dermis; inflammation due to matrix metalloproteinase; nociceptive and pruritogenic neuro sensory transmission from the skin via the DRG to the CNS, ultimately reached the cerebral cortex with the resultant perceptive symptoms; stress, emotional and psychological consequences of SSS secondary to the disarrhonnous secretions of cortisol via the hypothalamic-pituitary-adrenal axis.

**Female gender and atopic dermatitis**

The study in PMID 29370274 provides evidence that by visualizing the morphology of small nerve fibers in human skin biopsy; women have higher density of intraepidermal nerve fiber than men regardless of the age group [19]. PMID 26805416, this review further summarized SSS is more frequently observed in women; a consistent finding seen in most epidemiological studies [1,3,9-11]. As previously illustrated, intraepidermal nerve fiber correlated with up regulations of nerve growth factor in majority of organs involved in SSS like the skin, DRG, CNS, endocrine and gastro-intestinal tract. The increase incidence of female gender suffered from SSS may be genetically determined as the genetic predisposition of the two sexes have fundamental variations.

Atopic dermatitis is one of the skin diseases associated with SSS. The literature PMID 19443185 reviewed that atopic dermatitis patients have higher density of intraepidermal nerve fiber and expression level of nerve growth factor in skin [20]. Pruritus; the diagnostic and main clinical manifestation of atopic dermatitis; is suppressed by Psoralen-ultraviolet A (PUVA) therapy through decreasing intraepidermal nerve fiber densities and intensity of nerve growth factor in both epidermis and dermis [20]. In the review PMID 24628070 summarized similar findings on the distribution of nerve fiber and nerve growth factor in skin of atopic dermatitis patients [21]. Thus, as a chronic pruritic skin disease endowed with a genetic predilection of epidermal barrier defects; immune dysfunction and itch-scratch neuro-sensory abnormalities; atopic dermatitis has a similar clinical, molecular and pathogenetic mechanisms compared to SSS.

**Is there any evidence SSS pathogenetically linked to small fiber neuropathy?**

The arguments for neuropathic pain or neuropathy in SSS are scarce. More in depth, scientific, up dated, neurological, molecular and genomic investigations are needed to prove or disprove this axiom. In fact, apart from a few indirect literatures suggested SSS maybe of small fiber neuropatic nature, the author was unable to find any scientific study to substantiate this claim particularly on a genomic or molecular basis [14-16]. A research letter based on a validated questionnaire study was cited claiming that one-fifth of the patients with sensitive skin displayed characteristics of neuropathic pain [16]. This study is limited by the fact that the results are only found in severe SSS patients and the proportion of patients reported pain of neuropathic origin is less than one third. An epidemiological study based on a small sample size of less than one hundred recruited subjects solely on female gender without biological markers conferred a low degree of evidence to support the claim. Nevertheless, SSS is regarded as a prevalent global multi-organ involved condition; its pathogenetic basis should account for its frequent occurrence. Focal adhesions with its numerous assemblies of macro molecular proteins together with its genetic deficiency and polymorphisms and stress induced intraepidermal nerve fiber through increased production of nerve growth factor and TEWL may be a more convincing representation of the pathogenesis of this common and complex disease.

**Conclusion**

Our systemic review through Pubmed literature search failed to reveal published documented evidences and scientific proof of the direct relation of the pathogenesis of SSS to small fiber neuropathy. Instead, published evidences suggested genomics, focal adhesions regulating epidermal barrier, increased density of intraepidermal growth factor in various organs involving the epidermis, dermis, DRG, CNS and guts through mediation of nerve growth factor and TEWL are fundamentally involved in the pathogenesis of SSS. SSS is still a distressing, complex disease with significant health burden. More researches and scientific investigations and studies are needed to delineate the pathogenetic mechanism of SSS.

**References**


