International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 09, Issue 09, September 2024,
https://doi.org/10.23958/ijirms/vol09-i09/1960

Original Article

Mast Cells, Magnesium Chloride and Seborrheic Dermatitis as an Allergic Skin Disease

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Received 19 August 2024; Accepted 08 September 2024; Published 12 September 2024

Abstract

Seborrheic dermatitis is a dermatological syndrome which was first described in 1887 at about the time that tobacco smoking was becoming widespread in public places. Since 1978 the study of a familial seborrheic dermatitis revealed an immune reaction to the hapten nicotine of tobacco smoke. At that time, the efficacy of a sodium cromoglycate ointment showed a potential involvement of tissue mast cells. Later the use of a soap and ointment based on Dead Sea salts proved to be effective. At the same time, several laboratories detected histamine locally in patients afflicted with seborrheic dermatitis. Dead Sea and Zechstein salts contain about 30% of magnesium chloride. Recently, the use of a magnesium chloride ointment showed a significant efficacy. Future research should investigate the exact role of magnesium chloride on tissue mast cells and especially their ion channels. The stabilization of tissue mast cells appears as a new and promising research to help patients with seborrheic dermatitis and probably other dermatological syndromes as atopic dermatitis.

Keywords: ***seborrheic dermatitis; hapten nicotine; mast cells; histamine; magnesium chloride.***

Introduction

The dermatologist Unna described seborrheic dermatitis as a new facial dermatitis in 1887 [1]. He believed that this new dermatological syndrome was caused by the sebaceous glands in greater number in that area of the face. However, Paul Ehrlich described tissue mast cells for the first time in 1878 [2]. Dermatologists never made the link between tissue mast cells and seborrheic dermatitis during the twentieth century. Moreover, anaphylaxis was only discovered in the early 20th century by Richet and Portier [3].

However, after indentifying Malassez spores at the level of seborrheic dermatitis lesions, researchers then focused on the possible role of these skin saprophytes as a possible etiologic cause. In the late 19th century Rivolta, Malassez and Sabouraud conducted bacteriological studies on the presence of saprophytes of the scalp as pityrosporum. The presence on scalps affected with dandruff of pityrosporum was considered as another cause of the disease. On the other hand, Vidal opposed the fact that these spores are present on healthy scalp.

Karrenberg described in 1928 the case of a person with a facial dermatitis who worked in the tobacco industry and following contact with tobacco leaves, the application of one drop of nicotine diluted to one millionth had caused anaphylactic shock [4].

More than a century later, mast cells were confirmed at the base of the sebaceous glands. In his book "*Allergy at the dawn of the third millennium*" in 1997, immunologist Claude Molina described well the tissue mast cells around the sebaceous glands [5].

Seborrheic dermatitis as an atopic dermatitis

My familial dermatitis was first described in 1978 as an atopic dermatitis due to positive allergic tests (tobacco leaves patch test, tobacco leaves allergenic extract *Pasteur Institute* intradermal test 1/100.000, human basophil degranulation test tobacco and nicotine)[6].

At that time a leading article of *British Medical Journal* write that "*small amounts of nicotine inhaled by non-smokers are unlikely to have any medical importance*". My *Letter to the Editor* [7] summarized our familial atopic dermatitis induced by the hapten nicotine and the ongoing research at the Institute for Clinical Immunology in Bern, Switzerland. All sera of my family showed positive results with allergen tobacco and hapten nicotine when using passive cutaneous anaphylaxis tests in rabbits and guinea pigs.

All members of my family showed individual allergic reactions (asthma, urticaria, sinusitis) to a lot of allergens (i.e. *Dermatophagoides pteronyssinus*, povidone-iodine, oxprenolol, pristinamycin) and high total IgE antibodies for myself [8].

A specific desensitization with allergenic extracts of tobacco leaves (Pasteur Institute, Hollister-Stier) showed good results but was limited due to standardization of allergenic extracts [9]. In addition, overdosage induced symmetric skin reactions on both hands and arms.

A sodium cromoglycate ointment showed real effectiveness and potential involvement of the tissue mast cells at the origin of our familial dermatitis that resembled seborrheic dermatitis [10]. A stabilization of tissue mast cells appeared as a good solution to avoid side-effects of topical corticosteroids and the long-lasting desensitization.

Scientists were informed about the potential etiology of seborrheic dermatitis through publications in dermatology and toxicology reputable journals [11,12]. In addition, allergic investigations were positive for another patient afflicted with a facial seborrheic dermatitis [11] confirming tobacco as an allergen and nicotine as a hapten.

At that time, in their *Monograph on the pharmacology and toxicology of nicotine* the authors wrote that "*nicotine is not the responsible antigenic component of tobacco leaf although the possibility that nicotine could act as hapten cannot be excluded*" [13] (p. 19).

A century after the first description of a seborrheic dermatitis by Unna [1], the sebum excretion rate from forehead skin was measured in 44 patients with classic seborrheic dermatitis and 200 control subjects. The authors have found that the mean excretion rate was normal in the 29 men with seborrheic dermatitis and significantly reduced in the 15 women with the disease. They concluded that seborrheic dermatitis is not usually associated with seborrhea and therefore *dermatitis of the sebaceous areas* may be a more accurate term [14].

Nicotine was then clearly defined as a hapten and as possible cause of seborrheic dermatitis in a dermatology journal in 1984 [15].

Other authors have described a woman who reacted immediately after chewing a single piece of nicotine gum [16]. The major symptoms were nausea, flushing, pruritus, burning and erythema over the entire body and swollen lips described as the result of a nicotine overdose. In reality, the symptoms correlated with evidence of an anaphylactic reaction and such observation argue that nicotine can act as a hapten.

In 1985 I described a dermatitis of the hand and arm followed by a seborrheic dermatitis of the face after contact with nicotine of horsetails *Equisetum Arvense* L. [17].

Ketoconazole as an anti-leukotrienes

The successful use of topical ketoconazole as an anti-fungal treatment has been explained in the mid-1980s by its anti-leukotrienes properties in vitro, in vivo and by its capacity to inhibit the leukotrienes-mediated anaphylactic bronchoconstriction in the guinea-pigs [18]. I then explained the link between ketoconazole's local anti-allergic properties and its efficacy in seborrheic dermatitis[19].

The involvement of pityrosporum, a saprophyte of the skin present on all inflamed skin was refuted because solutions based on lithium succinate, a lithium salt have no activity [20] against this fungus showing that the origin of seborrheic dermatitis is probably allergic. In addition, how pityrosporum could jump from the face to the mid-thoracic area, another specific site of seborrheic dermatitis.

Nicotine as a hapten

In a review article on *tobacco smoke sensitivity*, S.B. Lehrer and colleagues concluded that *the presence of small molecular weight (dialyzable) components in smoke extract (possible haptens) can react with other proteins and serve as immunogens* [21]. S.B. Lehrer had previously detected a high level of specific IgE antibodies to tobacco leaves in my serum when using the Radioallergosorbent test (RAST). I have thus summarized in my letter to the editor of *Annals of Allergy* that *there is now evidence that, in some individuals, nicotine can act as a hapten and that its occurrence in passive smoking, botanic areas, foods at very low levels, smokeless tobacco, and chewing gums should be considered as a possible aetiologic factor in seborrheic dermatitis and probably other dermatologic reaction of unknown origin* [22].

Two other authors reported the case of a woman who reacted shortly after chewing a piece of nicotine gum [23]. The dermatological reaction was described as a perioral pruritic maculopapular rash. The patient had a history of hay fever and such observation argue again that nicotine can act as a hapten [24].

I had refuted a study by the famous British journal The Lancet in early 1989. The authors wanted to minimize the dermatological side effects of nicotine patches in 25% of patients with active patches (7.7 mg, 13.8 mg and 21.2 mg of nicotine) by comparing them with placebo patients (13%) that actually contained 1 mg of nicotine [25]. I informed the editor that a placebo should be neutral [26].

A chapter on the immunology of nicotine was published in the early 90 explaining that nicotine can act as a hapten and induce dermatological reactions in susceptible patients [27].

As a follow-up to a letter on potential interaction between niacin and transdermal nicotine [28], some information was published on the possible interaction between nicotine and niacin. Previous reports have described flushing and urticaria after intake of niacin and anaphylaxis after intravenous niacin [29].

Nicotine skin patch treatment and adverse reactions were ascribed as *skin irritation* [30]. A letter to the editor summarised the differences between skin irritation and skin sensitisation when using transdermal nicotine [31].

In 1998, researchers published confirmation of my work concerning the hapten nicotine without citing my research. A patient with recurrent generalized itching and urticaria due to inhalation of nicotine in tobacco smoke had symptoms and signs including generalized itching, weals and flares, and mild dyspneoa which occurred when he was exposed to tobacco smoke. After a positive intradermal nicotine test in this hypersensitive patient, they applied a nicotine patch which caused widespread hives [32].

In addition, the development of an anti-nicotine vaccine has ceased following several cases of anaphylactic shock [33] with specially one of the following descriptions: *One subject in the Phase IIb trial of the NicVAX vaccine had an allergic anaphylactic reaction that resolved with medication.*

A publication in the British Journal of Dermatology by Brazilian researchers demonstrate the lack of efficacy of ketoconazole against pityrosporum confirming that this fungus is only a saprophyte on the inflamed skin of seborrheic dermatitis [34].

More recently in 2018 at the faculty of Sarajevo a patient with seborrheic dermatitis reacted strongly by prick-test with nicotine while the investigators looked for a correlation between the different sources of sensitization and the individual predispositions of several patients [35].

Recently, multiple roles of cutaneous Malassezia in health and disease as commensal, pathogen, and protector have been discussed [36] and additionally the role of mast cells as a key factor for seborrheic dermatitis and atopic dermatitis has been suggested.

The connection histamine and mast cells

Researchers have linked the presence of histamine on the skin of seborrheic dermatitis in connection with itching in 2011 [37] also supporting my allergic theory and research with involvement of tissue mast cells [27]. Additionally, two recent publications have confirmed the presence of histamine locally [38,39].

These results confirm the potential involvement of tissue mast cells at the base of sebaceous glands for the origin of seborrheic dermatitis. In addition, some years ago, Felsenberg and Corrado were able to demonstrate that nicotine and other pyrrolidines induced the release of the components of the multivesicular granules of mouse neoplastic mast cells, including 5-HT (serotonin), histamine and heparin [40].

To confirm the major role of mast cells, a recent study found that 100µg/ml nicotine significantly induced mast cell degranulation and this phenomenon has been suppressed when pretreated by mast cell stabilizer disodium cromoglycate [41].

The help of Dead Sea salts

In March 2010, I had the opportunity to test a dermatological soap and ointment based on Dead Sea salts because it has long been known that patients with psoriasis see their skin reaction greatly improved in a Dead Sea spa treatment. After a few days of using these dermatological soap and ointment, I was surprised to see that my episodic reaction had disappeared. I only communicated this

positive information with two months of hindsight on one website dedicated to people with seborrheic dermatitis, later on a online health site and finally the summary on my Website [42]. With more than forteen years of hindsight, we now have hundreds of testimonials from people with seborrheic dermatitis and psoriasis (additionally some other dermatological diseases as dyshidrosis or atopic dermatitis) who have had a dramatic improvement in their skin reaction as summarized in my book *Towards a solution for seborrheic dermatitis* [43].

Magnesium chloride of Dead Sea and Zechstein salts

Dead Sea and Zechstein salts have a high concentration of magnesium chloride (about 30%) and previous research shows its potential to help improve skin conditions. Topical 5% Dead Sea salt magnesium for 4 days showed recently a significant improvement of symptoms [44]. Dead Sea and Zechstein salts magnesium can be a safe and effective treatment for seborrheic and atopic dermatitis by stabilizing tissue mast cells. Thus, we see that the first observation with a sodium cromoglycate ointment now joins a new observation with a Dead Sea and Zechstein salts ointment containing magnesium chloride. Currently, sodium cromoglycate topical extemporaneous compounding formulations are prepared in hospitals and community pharmacies of Spain [45]. These two ointment formulations are able to stabilize tissue mast cells thus preventing the release of allergy mediators such as histamine.

Magnesium and mast cells

In addition, previous work showing this key role of magnesium ions from the Dead Sea in dermatology was published in the early 90. Such research concerns on the one hand contact dermatitis and on the other hand the action of magnesium ions to block the release of leukotrienes from the cells of the allergy. In their 1990 publication [46], the researchers showed an inhibitory effect of magnesium ions to inflammation in contact eczema reactions. They examined the influence of Mg2+ on inflammation in 1-chloro-2,4-dinitrobenzene (DNCB) induced allergic contact dermatitis. Animals submitted to a 0.125% dose of DNCB in the presence of magnesium chloride (28% and 14%) had significantly less pronounced contact dermatitis (swelling of the ears). They confirmed these results in five nickel allergic patients, in whom magnesium chloride but not sodium chloride suppressed nickel sulphate-induced contact dermatitis.

The same group of researchers claimed that magnesium ions were responsible for skin anti-inflammatory action [47]. Their results suggest that high concentrations of Mg2+ inhibit eicosanoid metabolism, both at the level of arachidonic acid release and by direct inhibition of the enzyme 5-lipoxygenase.

Researchers published a study in 2016 showing that hair follicles promote the entry of magnesium ions into human skin [48]. Magnesium is an important micronutrient essential for various biological processes. Several inflammatory disorders in humans are related to a magnesium deficiency. Topical magnesium is one of the oldest forms of therapy for skin diseases, such as Dead Sea salt therapy and Epsom salt baths. Some published reports attributed the improvement in inflammatory skin conditions to topical application of magnesium. The main objective of the Australian researchers in this study was to estimate the extent of magnesium ion permeation through human skin and the role of hair follicles in facilitating permeation. When applied topically with a magnesium solution, they found that the magnesium penetrated into the human stratum corneum. This property depends on the concentration and time of exposure. They also found that hair follicles make a significant contribution to magnesium penetration. This research therefore supports us in the development of new magnesium-based solutions and creams.

The magnesium concentration remains to be determined in order to have an optimal stabilization of the tissue mast cells, knowing that a cream with 5% of Dead Sea salts contains about 30% of magnesium chloride.

As early as 1970, a publication by a Japanese researcher showed us the influence of calcium and magnesium ions on the stabilization of tissue mast cells [49].

Another Japanese publication from 1987 also demonstrates the importance of magnesium in preventing tissue mast cell degranulation [50]. Dermal mast cells in control rats were filled with granules, while cells of rats fed a magnesium-deficient diet for 4 days contained fewer granules than controls. These data suggest that hypomagnesemia may induce histamine release from dermal mast cells. Peritoneal mastocytes obtained on the 8th day of magnesium deficiency released much more histamine than controls in a 1 mM magnesium medium. These results suggest that the hyperemia observed in magnesium deficient rats is partly dependent on histamine released by dermal mast cells.

Magnesium in dermatology

Dermatologists were recently able to treat a pregnant patient with severe Darier disease using a magnesium chloride-calcium carbonate treatment as a monotherapy 2 tablets (MgCl2-CaCO3 71.5 mg- 119 mg) twice daily [51]. This disease is characterized by keratotic and crusted papules and plaques in a seborrheic distribution. Previously to this case report, other researchers described a Darier disease affecting a 11-year old patient. Conventional treatment was very limited and dermatologists decided to start a trial of oral magnesium chloride 300 mg per day. Within one-month, significant improvement was seen in lesions to the neck and temples [52].

Epidemiology versus observational medicine

Observational medicine has solved the etiology of a familial seborrheic dermatitis, an allergy to hapten nicotine and allergen tobacco since 1978. Based on this observation, an appropriate treatment aimed at stabilizing the tissue mast cells could be quickly implemented. Also, a targeted treatment with sodium cromoglycate and then with magnesium chloride of Dead Sea and Zechstein salts shows well the involvement of tissue mast cells at the base of the sebaceous glands.

Recently, epidemiological studies show a link of severity of seborrheic dermatitis in tobacco smokers [53,54]. At the same time another study has found a link between smoking and the severity of atopic dermatitis [55]. Also, it can be concluded that observational medicine is much faster to solve a skin disease in comparison with epidemiology [56]. Finally, a recent study of 2022 observed a causal relationship between allergy and seborrheic dermatitis [57] more than 4 decades after my first observation in 1978.

Conclusions

The long history of seborrheic dermatitis with unknown etiology since 1887 shows that initial hypotheses such as seborrhea and Malassez spores had no real scientific basis.

The personal and family history of allergies allowed to target on the one hand the allergen tobacco with the hapten nicotine and on the other hand the tissue mast cells at the base of the sebaceous glands causing histamine release.

A new strategy would be to test patients with seborrheic dermatitis systematically by nicotine prick-tests. Patients with atopic dermatitis and psoriasis may also be affected, as nicotine is present in tobacco smoke, vegetables [58] and other sources. Recently a study detected nicotine in boletes in South-East Europe for no apparent reason [59].

Such findings deserve further investigations in dermatology to replace the side effects of current therapies such as those of local corticosteroids for example. In conclusion, we can note the similarity of efficiency of sodium cromoglycate, magnesium chloride of Dead Sea/Zechstein salts and lithium gluconate or succinate, a lithium salt thus showing a probable action at the cellular level of these salts on the degranulation of tissue mast cells in presence of an allergen or an hapten. More focused research on ion channels is needed to elucidate the action of magnesium chloride in tissue mast cells.

Seborrheic dermatitis appears to be a specific form of atopic dermatitis induced by an hapten of the environment.

Declarations

Ethics approval and consent to participate

Not applicable in this section.

Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this paper.

Funding Statement

None

Authors' contributions

The author read and approved the final manuscript.

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