



Contact sensitization in the elderly

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Abstract Contact dermatitis from irritant and allergic sources is the reason for 6% to 10% of all dermatologic visits with considerable morbidity and economic impact. Allergic contact dermatitis is a T-cell-mediated inflammatory reaction and develops in predisposed individuals as a consequence of environmental exposure to allergens. Aging is correlated with the rate and type of contact sensitization because of “immunosenescence.” The number of old people is growing around the world. This contribution reviews the main findings from published epidemiologic studies on contact allergy in elderly populations. In all examined studies, patch testing was performed in patients with cutaneous manifestations possibly related to contact dermatitis; the prevalence of contact dermatitis in the elderly was from 33% to 64%. Establishing the most frequent allergens responsible for allergic contact dermatitis in the elderly is a hard task. The commonest allergens reported were nickel sulfate, fragrance mix, diamino diphenylmethane, lanolin alcohols, paraben mix, Euxyl K400, quinoline mix, and balsam of Peru. We emphasize that allergens surveillance is needed to realize an “elderly series” for having a useful adjunct to contact allergy that may help the treatment of each patient.

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Introduction

Life expectancy in industrialized countries has increased consistently in recent decades. In the United States of America, the proportion of people aged 65 or older increased from 4% in 1900 to about 12% in 2000. In 1900, only about 3 million of the country's citizens had reached 65. By 2000, the number of senior citizens had increased to about 35 million. It is estimated that more than 50 million Americans—about 17 % of the population—will be 65 or older in 2020.¹ The number of elderly people is growing around the world, so that provision and standards of health care are increasing too.

Pathogenesis of allergic contact dermatitis

Allergic contact dermatitis (ACD), one of the most common skin diseases with a great socioeconomic impact, is a T-cell-mediated inflammatory reaction (delayed-type hypersensitivity reaction) occurring at the site of challenge with a contact allergen (hapten) in sensitized individuals.² As in all delayed-type hypersensitivity reactions, the pathophysiology of ACD consists classically of two distinct phases: the sensitization and the elicitation phases, which are considered to be temporally and spatially dissociated.

The sensitization phase starts when haptens penetrate the skin. They are captured and conveyed by antigen presenting cells (APCs) to the draining lymph nodes, where they present haptenated peptides on major histocompatibility complex (MHC) class I and II molecules resulting in the induction of hapten-specific CD8+ and CD4+ T cells. The sensitization step lasts 8 to 15 days in humans and is thought to have no clinical consequence.^{2,3}

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In the effector or elicitation phase, the presence of even one antigen-specific T lymphocyte at the site of antigen reintroduction in the skin triggers an antigen-specific immunologic response to clear the antigen, with inflammation and tissue destruction manifested by ACD symptoms such as erythema, edema, and even blisters.² The efferent phase takes 48 to 72 hours in humans.

The inflammatory reaction persists during several days and progressively decreases upon physiologic downregulating mechanisms.²

Both Th1 and Th2 T cells are involved in ACD, but other cells such as natural killer T cells (NKT), natural killer cells (NK), and B1 cells contribute to the process and are essential for the efficient execution of the elicitation phase.³⁻⁵

Recently, it has also been reported that Th17 cells (lineage of T cells distinct from Th1 and Th2 cells) are involved in contact hypersensitivity (CHS) in murine models. Interleukin (IL)-17, the signature cytokine of Th17 cells, has been detected in human T-cell clones specific for nickel,⁶ and immune response to contact allergens was impaired in IL-17-deficient mice.⁷

The current opinion is that Th1 cells are the primary effectors, whereas Th2 cells are minor effectors in ACD/CHS.³ Most chemical haptens, such as dinitrofluorobenzene (DNFB), trinitrochlorobenzene (TNCB), and oxazolone, induce a Th1 response, whereas only some, such as trimellitic anhydride, induce a Th2-dominant CHS response.

Characterization of the new Th17 lineage and the study of its role in human ACD and murine CHS have helped to redefine the primary effectors in this disease. Thus, nickel-specific CD4⁺ clones isolated from humans can produce IL-17, which can enhance local inflammation in ACD by recruiting other cells and stimulating keratinocytes to elaborate proinflammatory cytokines.^{3,6} Cells that produce IL-17 are regular participants in the cellular infiltrates and thus might be important in the elicitation phase of ACD in humans.³

Although in some experimental systems CD4⁺ T cells have been shown to mediate the CHS responses,^{2,8} recent data substantiated the major role of CD8⁺ T cells as effector cells in CHS to different haptens.⁹ CD8⁺ T cells are the primary effectors in ACD, whereas CD4⁺ T cells play a regulatory role.^{3,10} It has been reported that both CD4⁺ and CD8⁺ subsets probably contribute to the ACD immune response because they both have the capacity to produce IL-17 and are present in significant numbers in the infiltrate.³

It has been well postulated that ACD is elicited by hapten exposure in sensitized individuals, but clinical evidence has demonstrated that "primary ACD" could develop in previously unsensitized patients. These reactions, known as "primary allergic reactions" or "active sensitization," develop 7 to 15 days after skin contact with potent contact sensitizers such as DNFB, urushiol, and primine.¹¹⁻¹³ The eczematous lesions are morphologically indistinguishable from conventional ACD and have the same kinetics in the amplification and the spontaneous regression of skin

inflammation, suggesting that similar effector and down-regulatory mechanisms are involved in classical and primary ACD. The relationship between primary and classical ACD has never been firmly established, however.²

Immunosenescence

The immune system of older people is usually perceived as declining in fidelity and efficiency with age, resulting in an increased susceptibility to infectious diseases and pathologic conditions relating to inflammation or autoreactivity.¹⁴ Immunosenescence is a term used to represent changes to the immune system associated with aging.¹⁵

Immunity is classically conceptualized as two distinct but interacting systems: innate and adaptive. Innate immunity may be thought of as the basal or first immune response, whereas adaptive immunity is a more specialized defence. Immunosenescence affects both innate and adaptive immunity. Aging is frequently associated with a decreased function of epithelial barriers of the skin, lung, or gastrointestinal tract, which enables pathogenic organisms to invade mucosal tissues, resulting in an increased challenge for the aged innate immune system.¹⁶

Phagocytic cells (neutrophils, monocytes, macrophages and dendritic cells), NK cells, soluble mediators such as cytokines, chemokines, hormones, and oxygen-free radicals are important in the innate immune system. The age-related changes that occur in neutrophils and macrophages include a decrease of oxidative burst, phagocytic capacity, and bactericidal activity.

Dendritic cells are involved in the innate and the adaptive immune system. They are professional APCs, being capable of capturing and processing antigens and of secreting a variety of cytokines. It is not yet completely understood how dendritic cells are affected by age. *In vivo* data from mice suggest that aged dendritic cells have an impaired capacity to stimulate antigen-specific T cells and that their *in vivo* trafficking to drain lymph nodes is affected by aging. In humans, the cell surface receptors are comparable between young and aged; thus, the defect appears to be in downstream signaling pathways.¹⁷⁻¹⁹

NK cells are important in the recognition of virally infected cells and in the rejection of tumors, and they are able to directly kill cells by releasing of cytotoxic perforin and granzymes. In senescence cells, cytotoxicity and interferon- γ production are decreased, but a defective functional capacity of NK cells is partially compensated for by an increased number of mature cells.^{16,20} These age-related defects in phagocytosis, killing, and migration could contribute to impairments in immunity in old age.¹⁶

Adaptive immunity includes antigen-specific cells such as B and T cells, cytokines, and cytolytic mediators, but also recruits components of innate immunity. Aging is associated with declines in overall T-cell number and function and shifts in subpopulation composition.¹⁵ This is largely due to the

accumulation of antigen-committed memory T cells and a decrease in naïve T cells capable of responding to new antigens.^{15,21} Other factors leading to T-cell dysregulation include age-associated changes in surface molecule expression, alterations in intracellular signalling, increased rates of apoptosis, and decreased proliferative capacity.²²⁻²⁴ Elevated plasma concentrations of IL-6, IL-1 β , and tumor necrosis factor (TNF)- α have been described in elderly populations and were postulated as predictive markers of functional disability, frailty, and mortality.^{16,17}

The B-cell compartment is also affected by aging; the quality of antibody response is substantially impaired. Recently, it was considered that the most likely cause of B-cell failure was a lack of effective T-cell help in a T-dependent reaction.¹⁶ Generation of B-cell precursors and number of naïve B cells are reduced with age, peripheral B-cell numbers do not decline with age, but the composition of the compartment, the isotype switch, and the antibody affinity change.^{16,25-29}

Antibodies generated in old age present lower affinity because of a shift in antibody isotypes from immunoglobulin (Ig) G to IgM.¹⁶ B cells from elderly individuals are stimulated 70% less efficiently by follicular dendritic cells than B cells from young people, suggesting loss of B-cell function as a result of the decreased expression of costimulatory molecules such as CD40 or CD27.²⁸ Aged CD4+ T cells produce less IL-2 and express less CD40L, which is crucial in the interaction of B and T cells. Less efficient T-cell help and the altered cytokine environment contribute to defects in antibody production.^{16,29}

Prevalence of contact sensitization in the elderly

Contact dermatitis from irritant and allergic sources is the reason for 6% to 10% of all dermatologic visits, with considerable morbidity and economic impact. This is aggravated by the fact that contact sensitization is not curable and necessitates lifelong avoidance of the allergens for secondary prevention.^{30,31}

Aging is correlated with the rate and type of contact sensitization, but only a few studies have evaluated patch test reactivity in elderly individuals with an adequately large population. The age range of elderly participants in different studies was between 69 and 76.2 years. In all examined studies, patch testing was performed in patients with cutaneous manifestations possibly related to contact dermatitis.³²⁻³⁷ The prevalence of ACD in the elderly is not similar in the literature, ranging from 33% to 64%.

An Austrian study in 1996 reported that the prevalence of positive reactions in elderly individuals was 33% for men and 35% for women.³³ A study group from Northern Italy reported that 40.7% of their elderly population showed positive reactions; of these, 68.2% were women and 31.8%

were men.³⁴ Our group from Southern Italy previously showed that at least one positive reaction developed in 41% of the sample, without a significant difference in the distribution by sex.³⁵ Another group from Central Italy found that the frequency of positive reactions in elderly patients was 43%, whereas 64.5% were women and 38.5% were men.³² An English study detected 59% of positive reactions.³⁶ In 2003, another group from Austria revealed a positive percentage of 34.9% in a sample aged older than 70 years.³⁷

Allergens

Establishing the most frequent allergens responsible of ACD in the elderly is a hard task. Here we report the prevalence of previously published studies on contact dermatitis in the elderly, focusing on the commonest allergens. The age and sex distribution of positive patch test reactions in 234 children, 1200 adults, and 295 elderly patients was investigated. Nickel sulfate and balsam of Peru were the most represented haptens, with 11.2% and 6.7% of positive reactions in old men, whereas they were respectively responsible for 12.6% and 9.7% of positive reactions in old women.³³

The British group compared patch test results in elderly patients of their center in two separate years (1982 vs 1997), with an interval of 15 years between. In 1982, the commonest allergens were topical antibacterials (20%), rubber accelerator (15%), fragrances and balsams (13%), and nickel (5%). By 1997, there was a decrease in topical antibacterials (9%), rubber accelerators (10%), and domestic antiseptics, with fragrances and balsams increasing dramatically (37%) and also nickel (9%).³⁶

The Austrian group patch tested 2776 consecutive patients (76.5% women) in 2003 with a locally revised standard series of 34 contact allergens, and the results were analyzed for age-specific and gender-specific differences. The commonest haptens in old patients were fragrance mix (11.2%), metallic mercury (8.6), nickel sulfate (8.6), balsam of Peru (5.3), and ethyl mercury (3.5%).³⁷ The rate of positive reactions to nickel and thimerosal decreased with age, whereas fragrance mix and metallic mercury were stable through all age groups. Reactions to nickel, cobalt, and palladium were significantly more common in women.³⁷

A retrospective study of 272 elderly patients found that nickel was the commonest sensitizer, followed by fragrance mix, paraphenylenediamine, and neomycin.³⁸ The group from Central Italy also reported a retrospective study of 224 elderly patients, showing that the most frequent allergens were nickel sulfate, especially in women, balsam of Peru, and topical medicaments, with no difference between the sexes; potassium dichromate, mostly in men and fragrance mix, chiefly in women.³²

The northern Italy group studied 1444 elderly individuals and compared the results with a control group of individuals

with suspected ACD, aged between 20 and 40 years. The prevalence of the positive patch test to at least one hapten was significantly lower in the elderly patients compared with adult patients (40.7% vs 47.8%). The most frequent contact allergens in the elderly were nickel sulfate (6.9%), fragrance mix (4.8%), balsam of Peru (4.6%), and potassium dichromate (4.5%). They found, moreover, that some allergens (eg, primin, diamino diphenylmethane, neomycin, lanolin alcohols, paraben mix, Euxyl K400, and quinoline mix), showed an increased sensitization rate in elderly patients compared with adult patients.³⁴

We reported data for 117 elderly individuals, and 48 (41%) developed at least one positive reaction. ACD was detected in 13% of our sample. The five most frequent allergens were nickel sulfate (13.7%), potassium dichromate (11.1%), cobalt chloride (7.7%), paraphenylenediamine (5.2%), and balsam of Peru (4.3%).³⁵ In a recent study, 2076 patients (1375 women and 701 men) were patch tested. The age-related trends for the top four allergens, for men and women combined and separately, showed that nickel sulfate and cobalt chloride prevalence decreased with age, whereas balsam of Peru increased with age. Neomycin, thiuram mix, and colophonium contact allergy increased with age in women, whereas in men, only colophonium increased, but neomycin remained stable. Para-phenylenediamine sensitivity remained stable in both sexes.³⁹

The differences observed in these studies could be dependent on several parameters. The importance of age, sex, race, and occupation has been well established, and here they represent a limit to compare results of different studies. Geographic factors, atopic dermatitis, and even seasonal parameters can also influence skin reactivity.³⁷⁻⁴¹ Some common sensitizers are, therefore, of worldwide relevance and are the basis for the standard series, but some contact allergens, such as thimerosal, are not equally important in all areas,³⁷ so that standard series are locally modified. Nickel sulfate^{32,35,38,39} and fragrance mix,^{33,34,37} however, were the most widespread haptens. The commonest allergens in the elderly are summarized in Table 1.

Nickel sulfate

Nickel sulfate remains one of the commonest allergens in the elderly. This can be explained by its ubiquity in the environment, but there is the possibility of persistent historical sensitizations to nickel allergens that either no longer occur in the general environment or are no longer clinically relevant.³² Hypersensitivity to the metals nickel, cobalt, palladium, and copper steadily decreased with age in the Austrian population.³⁷ These data fit with the Northern Italy study, where a lower prevalence of nickel sensitivity older patients with respect to adults (6.9% vs 24.2%) was described.³⁴ Similar results also occurred in our study, where the nickel positivity was distributed by 13.7% in elderly patients and 24.6% in adult patients.³⁵

Table 1 The commonest allergens in the elderly reported by different studies

First author	Finding
Wantke, ³³ 1996	Nickel sulphate (11.2%), balsam of Peru (6.7%; men); nickel sulphate (12.6%), balsam of Peru (9.7%; women)
Gupta, ³⁶ 1982	Topical antibacterials (20%), rubber accelerator (15%), fragrances and balsams (13%), nickel sulphate (5%)
Gupta, ³⁶ 1997	Fragrances and balsams (37%), rubber accelerators (10%), topical antibacterials (9%), domestic antiseptics, and nickel sulphate (9%)
Wohrl, ³⁷ 2003	Fragrance mix (11.2%), metallic mercury (8.6%), nickel sulfate (8.6%), balsam of Peru (5.3%), ethyl mercury (3.5%)
Onder, ³⁸ 2003	Nickel was the commonest sensitizer, followed by fragrance mix, paraphenylenediamine, and neomycin
Tosti, ³² 2004	Balsam of Peru and topical medicaments (no difference between sexes); nickel sulphate and fragrance mix (women); potassium dichromate (men)
Piaserico, ³⁴ 2004	Nickel sulphate (6.9%), fragrance mix (4.8%), balsam of Peru (4.6%), and potassium dichromate (4.5%)
Balato, ³⁵ 2008	Nickel sulphate (13.7%), potassium dichromate (11.1%), cobalt chloride (7.7%), paraphenylenediamine (5.2%), and balsam of Peru (4.3%)

Fragrance mix

Sensitization to fragrance chemicals is thought to result from repeated encounters with perfumed products, which are ubiquitous in daily life. Owing to cumulative exposure, it would be reasonable to expect that the frequency of fragrance allergy might increase with advancing age.⁴²

During the seventh decade in women and in the eighth decade in men, a steep increase in the rate of sensitization to fragrance in patch-tested individuals was found. Possible explanations may include impaired skin barrier function due to asteatotic dermatitis on the lower limbs and increased use of local medicaments that may contain fragrance. It is important to underline that in the very elderly, there was a decline in rates of sensitization. Previously sensitized patients were perhaps no longer able to mount an immune response to fragrance. It is unlikely that these patients suddenly develop active tolerance and more likely that this is a manifestation of the decrease in the induction and elicitation of ACD that occurs in old age.^{15,16,42}

Topical agents

Allergens such as diamino diphenylmethane, lanolin alcohols, paraben mix, Euxyl K400, quinoline mix, and

balsam of Peru showed higher sensitization rate in the elderly compared with adults. Diamino diphenylmethane is used in rubber products and may usually be used in elastic bandages or in the management of stasis dermatitis.³⁴ Lanolin alcohols have been used for many centuries as medicinal and skin care products,⁴³ and parabens and Euxyl K400 are important preservatives.⁴⁴ Several studies have suggested that the prevalence of contact allergy to these haptens is low among healthy individuals⁴⁵ but is high when these substances come in contact with inflamed or ulcerated skin.^{43,44}

Neomycin, clioquinol, and fusidic acid are all topical antibiotics used in dermatologic practice.⁴⁶ A 2002 study compared the frequency of allergic reactions to these three drugs.⁴⁶ The frequency of medicament allergy to neomycin was approximately 5 times more common than to clioquinol, and 10 times more common than to fusidic acid. The demographics were similar for all three antibiotics, with topical antimicrobial sensitivity being more prevalent in women, apart from clioquinol, possibly due to the poor cosmetic acceptability of yellow-staining creams.⁴⁶

Contact sensitization in elderly patients with leg ulcers

Leg ulcers represent a chronic condition affecting more than 1.7% of the population aged older than 65 years.⁴⁷ Many topical medications are used for leg ulcers, so some have proposed that patients with chronic leg ulcers should be tested because they have a very high risk of contact allergy. Their sensitization rate increases with the duration of the chronic leg ulcers. In 1185 cases published from 1991 to 2003, 72% had a positive patch test. This meta-analysis was undertaken on studies from January 1, 1975, to July 30, 2003. The principal haptens in 3043 leg ulcer patients (1858 patients [1975–1990] vs 1185 patients [1991–2003]) were lanolin (22.9% vs 17.5%), balsam of Peru (16% vs 25.4%), aminoglycoside (13.1% vs 13.9%), fragrance mix (10.7% vs 18.8%), and thiuram mix (3.1% vs 5.5%).⁴⁸

The prevalence of allergen sensitivity in patients with past or present leg ulcers was compared with European study findings and the North American Contact Dermatitis Group (NACDG) database. Their results showed that 63% of the patients had one or more allergen sensitizations.^{49,50} From the comparison with NACDG data, they found that patients with leg ulcerations had higher frequencies of positive contact sensitization to balsam of Peru (30% vs 12%), bacitracin (24% vs 9%), fragrance mix (20% vs 11%), propylene glycol (14% vs 4%), and carba mix (11% vs 5%). The frequency of contact sensitization to nickel was higher in the NACDG database (16% vs 11%). They also compared the most frequent allergens in their study group with European studies and found the following differences in allergen sensitization: balsam of Peru (30% vs 3.4%–40%), bacitracin (24% vs 13.1%), fragrance mix (20% vs 7.4%–

28%), wood tar mix (20% vs 1.8%–15.0%), propylene glycol (14% vs 0%–8.3%), neomycin (13% vs 2%–34.0%), benzalkonium chloride (13% vs 2.8%–15.32%), carba mix (11% vs 1.7%–8.6%), nickel (11% vs 0%–16.7%), formaldehyde (9% vs 0.67%–8.0%), Quaternium-15 (9% vs 0%–4.9%), lanolin (9% vs 8.5%–33.3%), Euxyl K400 (9% vs 0%), and hydrogel with propylene glycol (9% vs 8.3%).⁴⁹

Features of contact sensitization in the elderly

This section summarizes the main findings from published epidemiologic studies on contact allergy in old populations. Contact allergy is caused by skin contact with low-molecular-weight haptens and may evolve to allergic contact dermatitis if exposure exceeds the individual's threshold. It can be a distressing skin problem for those who have it and may cause sick leave as well as an increase in national health expenses. The diagnosis of contact allergy is mainly determined by the outcome of patch testing; however, a positive test reaction is not necessarily an indicator of clinical disease, that is ACD, because the patch test only measures whether the individual is sensitized.⁵¹

In tracking down the cause of contact dermatitis in the older age group, not only must the physician question the patient concerning new contactants, but a thorough investigation must also be made of substances to which the patient has been exposed for decades. It is surprising how frequently the older patient becomes sensitized to a contactant to which he or she has been exposed intermittently thorough life without any previous reaction. Properly performed patch tests are reliable in finding the causative agents in ACD in people of this age group too.⁵²

The disease in older people, even during the acute stage, may show relatively little vesiculation or inflammation. Scaling is regularly a prominent feature in all phases of contact dermatitis in the elderly. Thickening, hyperpigmentation, and lichenification take place readily, and itching is usually pronounced. Allergic and irritant eruptions both tend to persist and be more resistant to therapy in aged individuals than in younger people.

The hypothesis of a slower immunologic reactivity in elderly patients fits with the dynamic reaction pattern course. Three dynamic reaction patterns can be distinguished: stable (day 2 grade = day 3), increasing (day 2 grade < day 3), and decreasing (day 2 grade > day 3).^{34,35} In our study, 64% of the patients showed a dynamic pattern of increasing intensity (day 2 < day 3), in accord with Northern Italy group, who found this pattern in 60% of elderly patients vs 53% of the younger population.^{34,35} Because human aging is accompanied by a decline in immune function, the individual's ability to react to a contact allergen may be slowed down, and an additional patch-test reading between day 5 and day 7 should be considered.³⁴⁻³⁶

Conclusions

Apart from the controlled and retrospective studies of a large population reviewed here, several reports about ACD in older patients have highlighted that contact sensitization is also a burden problem in the elderly. Allergens surveillance is needed to realize an "elderly series" for having a useful adjunct to contact allergy, which may help in tailoring the treatment for each patient.

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