AGE-RELATED IMMUNOSENESCENCE AND TOTAL SERUM IGE DYNAMICS IN GERIATRIC DERMATOMYCOSES

Artizana Dushi
Faculty of Medical Sciences, Goce Delcev University, Štip, North Macedonia,
artizane.311119@student.ugd.edu.mk
ORCID ID: 0009-0007-4992-6145
Dance Vasileva
Faculty of Medical Sciences, Goce Delcev University, Štip, North Macedonia,
dance.vasileva@ugd.edu.mk,
ORCID ID: 0009-0006-1072-432X
Sotirija Duvlis
Faculty of Medical Sciences, Goce Delcev University, Štip, North Macedonia,
sotirija.duvlis@ugd.edu.mk
ORCID ID: 0000-0001-8587-7386

Abstract: Superficial fungal infections diagnosed in elderly individuals commonly become chronic and respond poorly to treatment, resulting in suboptimal clinical treatment outcomes. Age-related immune senescence is characterized by weakened cell-mediated immunity with particular emphasis on the Th1 and Th17 pathways which play an essential role in the host's response to fungal infections. Nonetheless, the correlation between the total serum immunoglobulin E (IgE) levels and the superficial fungal infections in the cases of non-atopic geriatric patients remains inadequately characterized. This study aimed to compare the total serum IgE concentrations between older and younger patients diagnosed with superficial fungal infections.

A total of twenty-five non-atopic patients with confirmed superficial fungal infections through microbiological techniques involving fungal culture and potassium hydroxide microscopy (KOH) were categorized in two groups: Group 1 consisted of 13 older patients (≥65 years, n = 13) whilst Group 2 included 12 younger patients within the ages of 18-45 years old. Through the usage of chemiluminescent immunoassay (CLIA), total serum IgE concentrations of all the patients were determined with values below 100IU/mL being considered normal. It should be noted that entities with allergic rhinitis, eczema or parasitic infections were not included in the study, to minimize the confounding factors which might affect IgE levels.

In the geriatric group with a percentage of 69.2, 9 out of 13 patients presented with elevated serum IgE levels (>100IU/mL) as opposed to a 25.0 percentage with 3 out of 12 patients in the younger cohort ($p = 0.047$). Furthermore, in the elderly cohort, mean serum IgE concentrations were markedly higher than in the younger cohort with the following statistics for group 1; 462.8 ± 105.4 IU/mL, and Group 2 135.2 ± 38.6 IU/mL; $p < 0.001$. A longer disease duration was noted in Group 1 patients as well (3.1 years vs 0.5 years). in 72.0% of the cases in both groups, the predominant etiological organism was Trichophyton rubrum. Moreover, a strong association was identified between serum IgE concentrations and increasing age ($p = 0.001$, $r = 0.612$).

The age-related deterioration in cell-mediated antifungal immunity may promote a Th2-biased immune response, resulting in an increase serum IgE concentration in patients, independent of atopic disease. This immunological response presents a great shift which may play a role to chronicity as well as persistence of superficial fungal infections in older adults. Therefore, the assessment of baseline serum IgE measurement provides a great and valuable adjunctive biomarker for labeling older adult patients who are more likely to benefit from prolonged as well as intensified antifungal treatment.

Keywords: Dermatomycoses, Total Serum IgE, Immunosenescence, Geriatric Dermatology, Trichophyton rubrum

1. INTRODUCTION

New challenges to clinical dermatology are being introduced with the aging global population, concerning the high prevalence of chronic skin conditions in older adults. Prominent among them are superficial fungal infections, specifically those that arise from dermatophytes, which present a significant challenge (Gupta et al., 2021). Fungal manifestations such as onychomycosis and tinea pedis are very often overlooked in older adults as benign cosmetic concerns even thorough they routinely serve as persistent microbial reservoirs. Furthermore, if they remain undiagnosed and consequently untreated, these infections can be the leading cause of skin breakouts, secondary bacterial cellulitis as well as significant functional impairment (Hay, 2018; Leung et al., 2020).

Immunosenescence presents a steady restructuring of the adaptive and innate immune systems as a result of aging. In the cases of cutaneous tissue, this shift presents as lower Langerhans cell density, epidermal thinning, slower cell turnover and most importantly a weaker T-cell receptor signaling. Most critically, the cellular

immune axis identified through Th1 and Th17 responses, which release Interferon-gamma (IFN-γ) and Interleukin-17 (IL-17)- lowers greatly concurrent with age. Due to the fact that Th1-Th17 cell-mediated immunity is our primary protection and agent for clearing dermatophyte from the areas of stratum corneum, this linked to advancing age drop left older adults susceptible to hard to clear persistent chronic fungal infections (Brasch, 2010; Calderón & Hay, 2019; Zapata & Shaw, 2023)

While cellular clearance mechanisms weaken, the deteriorating immune system in older adults very often presents dysregulated humoral response. Even though classic atopic conditions such as bronchial asthma and atopic dermatitis are most common in younger adults, older individuals can also present isolated elevations in total serum immunoglobulin E (IgE) despite lacking any clinical evidence of local or systemic allergy (Korting & Zienicke, 1990).

This study presents a thorough investigation as to whether the age-related T-cell immune senescence triggers a secondary, unguided Th2 humoral shift In non-atopic host environment, investigating whether total serum IgE can serve as a diagnostic tool for long-standing infections in aging populations.

2. MATERIALS AND METHODS

A clinical cross-sectional pilot investigation was conducted, to address the objectives of this research consisting of a total 25 non-atopic adult patients, all of whom with active clinically suspected and subsequently mycologically verified superficial dermatomycoses.

The patient group was divided into two distinctive age groups:

- Group 1; named Geriatric Cohort with a total of 13 patients all of whom aged ≥ 65 years old with a mean age of 71.8 ± 5.2 years
- Group 2; named Younger Control Cohort with a total of 12 patients aged 18 to 45 years old with a mean age of 32.1 ± 6.1 years

To provide insurance that the observed relationship between the IgE dynamics, fungal infection and age-related immune senescence was not influenced by unrelated or external immunological factors, a detailed and thorough set of exclusion criteria was implemented prior to the patient's recruitment. These criteria were established to reduce the impact of treatments and conditions recognized to influence the immune response or affect the IgE production, thus improving the internal validity of the study as well as reduce the influence of confounding factors.

Patients were not included in the study in the event that they had a family or personal history of atopic diseases which include but are not limited to atopic dermatitis, allergic rhinitis bronchial asthma, as these pathological conditions are directly linked with elevated IgE levels and alter immune function. Patients with active peripheral blood eosinophilia ($> 0.5 \times 10^9/\mathrm{L}$) were also rejected from the study due to eosinophilia indicating possible underlying inflammatory allergic or parasitic conditions that might obscure the true immunological response under investigation. To maintain a controlled study cohort and reduce possible sources of bias, potential patients that had documented tissue or intestinal parasitic infections were excluded. The parasitic infections were confirmed through the usage of stool microscopy, taking into account that these infections are well known to substantially increase IgE levels and eosinophilia, which could influence the assessment of immune responses that are linked with fungal infections.

Furthermore, patients who had previously received immunosuppressive medications, systemic corticosteroids or systemic antifungal therapy within the last three months were not included, as these treatments trigger a series of immunological effects events such as; suppression of inflammatory responses, alterations of the fungal burden or modify the immune function

In order to carry out the microbiological assessment of the fungal infections in the selected patients, clinical specimens were obtained from the active margins of lesions through the usage of sterile curettes. Nail clipping followed by epidermal scrapings were taken from the active margins as well to maximize the likelihood of taking viable fungal elements. These samples were assembled very carefully as to avoid any possible contaminations and were processed usings a series of direct microscopic examination and fungal culture techniques. A dual diagnosis approach comprising culture-based isolated methods and direct microscopy was carried out in order to complete the laboratory identification of fungal pathogens. The collection of tissue fragments was processed through the usage of 10% potassium hydroxide (KOH) solution and afterwards examined under light microscopy in order to detect the fungal structures, and the branching septate hyphae, which suggests the presence of fungal infection. The clinical samples were inoculated onto Sabouraud Dextrose Agar (SDA), supplemented with chloramphenicol (0.05g/L) in order to assist the fungal growth whilst reducing the unwanted microbial growth. These cultures were incubated at 28°C for up to 21 days, thus enabling sufficient time for the development of fungal colonies. Afterwards, fungal isolates were identified based on their microscopic characteristics and colony appearance and then the species identification was carried out using slide cultures technique.

For the immunoassay quantification, through aseptic venipuncture, venous blood samples (5ml) were drawn and collected into serum separator tubes in order to guarantee proper sample preparation. In order to perform

immunological analysis, these collected samples were centrifuged at 2,000 x g for a duration of 10 minutes and analyzed immediately. The total serum IgE concentrations were measured via standardized Chemiluminescent Immunoassay (CLIA) platform. Any values less than 100 IU/mL were referred to as normal, whilst values exceeding 100 IU/mL were marked as elevated (Perea et al., 2021).

To conduct statistical analysis SPSS statistics (Version 28.0) were executed. The quantitative values were defined as mean $\pm$ standard deviation (SD), furthermore, the continuous parameters between the defined Groups1 and 2 were assessed through independent-samples t-tests. For the analysis of the categorical data Pearson's Chi-square (χ^2) test was used, or Fisher's Exact test where applicable. Finally, to provide a definite evaluation between the serum IgE levels, disease duration as well as advancing age, Spearman's rank correlation coefficient (r) was applied. The statistical threshold of $p < 0.05$ was set.

3. RESULTS

The cohort contained 13 males representing 52.0% and 12 females with 48.0%. The sex composition of the patients was relatively balanced with no statistical significance observed ($p = 0.850$). However, a difference was noted in the time frame of the fungal infection duration between these age groups, with the geriatric group (Group 1) having a notably longer mean infection 3.1 ± 1.2 years, in comparison to the Group 2 with 0.5 ± 0.3 years. Due to this alteration being statistically proven significant ($p < 0.001$), it has been indicated that the geriatric group has had an active infection for a substantially longer period.

Furthermore, the clinical presentation of the fungal infection also proved of great difference between the two groups. To elaborate this further in Group 1, onychomycosis and tinea pedis was a combination that occurred in most clinical presentations with a percentage of 61.5 (n = 8) of the cases. By contrast, in Group 2 a predominant clinical presentation was notes with tinea corporis and tinea cruris with a percentage of 75.0 (n = 9), These results present clear differences in both the clinical presentations as well as the duration of fungal infection between the age groups.

Table 1. Baseline demographic, clinical, and immunological parameters of the study cohort

Clinical Parameter	Geriatric Cohort (≥65 yrs, n=13)	Younger Cohort (18–45 yrs, n=12)	p-value
Mean Age (Years ± SD)	71.8 ± 5.2	32.1 ± 6.1	< 0.001
Sex (Male / Female)	7 / 6 (53.8%/46.2%)	6 / 6 (50.0%/50.0%)	0.850
Mean Infection Duration (Years)	3.1 ± 1.2	0.5 ± 0.3	< 0.001
Elevated IgE (> 100 IU/mL)	9 (69.2%)	3 (25.0%)	0.047
Mean Serum IgE (IU/mL)	462.8 ± 105.4	135.2 ± 38.6	< 0.001

Source: Primary clinical and laboratory dataset from the cross-sectional pilot investigation conducted at the Faculty of Medical Sciences, Goce Delcev University (2024–2025).

The growth of the fungal culture was detected in 23 out of 25 total cases, presenting a percentage of 92.0 of all the participants. The most common fungal species identified in the study was Trichophyton rubrum with 72.0%in n = 18, followed by *Trichophyton mentagrophytes* with 20%, n = 5, and the remaining 8.0% with n = 2 were culture negative nonetheless, presented positive results in the KOH examination. There was no statistically considerable difference detected in the distribution of the fungal pathogens identified between the age cohorts ($p = 0.610$).

A great statistical difference was presented by the immunological testing concerning the IgE levels between the age groups

- In the geriatric group (Group 1) 69.2% of patients 9/13, presented high total serum IgE concentrations (> 100 IU/mL)
- In the younger group (Group 2), higher serum IgE concentrations were identified in solely 25.0% of patients (3/12) ($\chi^2 = 4.88, p = 0.047$).

A further difference was obtained in the mean total serum IgE concentrations between the groups, with Group 1 having a markedly higher mean (462.8 ± 105.4 IU/mL), whilst Group 2 had a mean concentration of (135.2 ± 38.6 IU/mL). This variation was statistically considerable in accordance with the Students' test, $t = 10.34, p < 0.001$

For the correlation analysis through the Spearman rank correlation testing, it was verified that there was a strong association between the advancing age of the patient and the total serum IgE levels ($r = 0.612$, $p = 0.001$). Furthermore, a positive correlation was noted in the IgE levels with overall disease duration ($r = 0.544$, $p = 0.005$), presenting that a longer fungal infection in older patients may be linked with sustained systemic humoral immune responses.

4. DISCUSSION

The proper medical management of superficial fungal infections in older patients necessitates a more thorough understanding of the alterations that may occur in the immune system in accordance with age. In this study, elderly patients aged ≥ 65 years with superficial fungal infections, presented substantially higher total serum IgE levels when compared with younger participants aged 18-45 years old. This increase in intensity was noted regardless of the absence of clinical signs of atopic disease amongst the participants.

In the cases of younger healthy individuals, dermatophyte clearance is led by cell-mediated immunity. Upon recognition of fungal cell wall antigens (e.g mannan, β-glucans), by dermal dendritic cells the Th1/Th17 cascade is induced. The release of IFN - γ triggers macrophages and stimulates the keratinocyte proliferation, permitting the physical desquamation of the infected epidermal layers

Conversely, biological aging impacts the protective cellular immune response which oversees the fungal infections (Monod & Fratti, 2022; Shiraki et al., 2006; Vermout et al., 2008). Alterations that are linked to aging such as thymic involution, and a lower production of IFN – γ, may weaken the body's ability to clear fungal infections. When T.rubrum lingers within the stratum corneum for a sustained period, persistent exposure to fungal antigens may maintain the immune activation and lead to a shift toward a more Th2 dominant response (Arora & Sardana, 2022). This move may support a Th2 dominated response with increased production of IL-4 and IL-13, which stimulate B cells to produce elevated IgE levels, Nonetheless, the higher IgE response may not be enough to remove dermatophyte infections efficiently from the outer layers of the skin. Subsequently, these fungal infections stay longer in the skin, whilst persistent exposure to fungal antigens may influence the maintenance of elevated systemic IgE levels. This mechanism may help explain why older patients in this study presented both longer infection duration as well as higher IgE levels in comparison to younger patients (Schaller & Korting, 2007).

The afore-mentioned empirical findings provide a well-defined therapeutic and diagnostic implications such as; diagnostic biomarker interpretations and therapeutic optimization. To elaborate on this further; higher total serum IgE levels in geriatric patients with fungal pathogenies should not be necessarily linked to late-onset atopy or even environmental allergies, instead, they indicate that there is a reduced cell-mediated clearance of the fungal infections and a great probability of prolonged fungal persistence. Furthermore, due to the fact that older individuals with higher baseline IgE encounter a prolonged infection course (3.1 years average in this cohort), the benchmark brief topical medical therapies are often not enough. These individuals would greatly benefit from longer-term systemic antifungal medications paired with careful clinical monitoring which might include but is not limited to; itraconazole or oral terbinafine, concurrent with topical keratolytic remedies and measures directed toward preserving the skin's natural barrier (Goyal et al., 2022).

5. CONCLUSION

In non-atopic geriatric patients with superficial dermatomycoses a higher total serum IgE level was present as opposed to younger adults aged 18-45

Furthermore, in regards to the immunological changes; these conclusions indicate that the age-related alterations in immune function can be linked with a shift towards a less adequate humoral response, which is reflected by the elevated IgE levels and the prolonged fungal infection. Nonetheless further studies are of necessity to further shed light on these immunological alterations and how they directly influence the fungal persistence in geriatric patients. Most importantly, the measurement of baseline serum IgE presents a objective and practical additional yet vital biomarker for evaluating geriatric patients with fungal infections. Its role in detecting patients who may need closer monitoring or a longer medical therapeutic management should be investigated further.

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