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ORIGINAL ARTICLE

Investigation of underlying primary immunodeficiencies in patients with severe atopic dermatitis

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Abstract
Background: Primary immunodeficiency diseases (PIDs) are a group of heterogeneous inherited disorders, characterised by recurrent infections, autoimmunity and malignancy. Some PIDs such as hyper IgE syndrome (HIES) and Wiskott–Aldrich syndrome (WAS) may be initially presented as atopic dermatitis (AD), especially in its severe form, resulting in diagnostic delay and poor prognosis of patients.
Objective: The aim of this study was to evaluate the frequency of PIDs among patients with severe AD and to determine factors that can help to raise suspicion towards these disorders.
Methods: Seventy-five patients with a well-established diagnosis of severe AD were enrolled in this study. Initial immunological evaluations, including humoral and cellular investigation, were performed in all individuals. Patients underwent further investigations in a case of suspicion of a probable PID.
Results: Among all patients with severe AD, five (6.6%) were diagnosed with HIES and one (1.3%) with WAS. Family history of PIDs, family history of death in early infancy, positive history of recurrent infections such as skin and respiratory infections, otitis media and sinusitis were observed significantly higher in patients with a diagnosis of PID.
Conclusions: The presence of an underlying PID could explain the poor prognosis and refraction to the treatment of some patients with severe AD. Several clinical and laboratory findings can help the physicians to focus towards PIDs which are more serious. Delay in diagnosis of PID cases with skin manifestation of AD without proper management may result in lower quality of life and higher morbidity and mortality rates.

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Introduction

Primary immunodeficiency diseases (PIDs) are inherited disorders that predominantly affected infants and children, which are usually characterised by recurrent infections of different organs as well as autoimmunity and malignancy in some cases.[1,2] Skin is one of the organs that can be involved in PIDs and its complications include infections and abscesses (e.g., in severe combined immunodeficiency, chronic mucocutaneous candidiasis, and phagocyte defects), poikiloderma (e.g., in poikiloderma with neutropenia), erythroderma (e.g., in Omenn syndrome), anhydrotic ectodermic dysplasia (e.g., in NEMO deficiency, autosomal-dominant anhydrotic ectodermal dysplasia with immunodeficiency, calcium channel deficiency with ORAI-I deficiency and STIM-1 deficiency), keratinocytes defect with human papilloma virus infections and cancer of the skin (e.g., in epidermodysplasia verruciformis) eczematous dermatitis, petechiae, vasculitis and autoimmune skin disorders (e.g., in predominantly antibody deficiency) which may be the clue for the final diagnosis of a PID.[2–5]

Atopic dermatitis (AD) is a common eczematous skin disorder which mostly occurs during the infancy and childhood, characterised by intense itchy, erythematous papules, vesicles, and oedema in acute stages and lichenification in chronic stages. It is also associated with increased serum IgE levels.[6,7] Patients with the severe form of AD do not effectively respond to conventional treatments of this disorder such as oral antihistamines and topical corticosteroids[8]; therefore they need systemic immunosuppressive agents and to search for the cause of severity.[9,10]

Eczematous dermatitis resembling severe AD occurs frequently and is associated with a few types of PIDs, including selective IgA deficiency, common variable immunodeficiency (CVID), Wiskott–Aldrich syndrome (WAS), X-linked agammaglobulinaemia, hyper IgE syndrome (HIES), and Omenn syndrome.[4,6,11–13]

The presence of a PID in patients with severe AD should be investigated, since severe AD can be the first presentation of these disorders. Timely diagnosis and management of patients with PIDs are of significant importance and delay in diagnosis is associated with higher rates of morbidities and lower quality of life, especially in cases with non-infectious manifestations.[14–16]

There are no specific data on the prevalence of a PID in subjects presenting with severe AD. Moreover, co-factors that help in clinical suspicion of a PID in severe AD phenotype are not completely identified. We studied patients with severe AD to investigate presence of PIDs in these patients assessing their clinical and laboratory findings.

Patients and methods

Patients

Between March 2010 and April 2011, all qualified patients who visited the Department of Dermatology at the Razi Hospital and the Department of Immunology at the Children's Medical Center Hospital (Tehran, Iran) with a well-established diagnosis of severe AD were enrolled for immunological evaluations. Both hospitals are affiliated to Tehran University of Medical Sciences. Patients with a known secondary immunodeficiency were excluded from the study.

According to the Hanifin & Rajka criteria,[6] the diagnosis of AD is proven with at least three major criteria including: itching, lichenification (flexor and linear surfaces in adolescents and extensor surfaces lichenification in children), chronic or recurrent symptoms, atopy (asthma, allergic rhinitis, atopic dermatitis) past or family history, and three minor criteria including: skin dryness, cheilitis, fissure, etc. AD was defined as severe, when the calculated value of the severity scoring system for AD (SCORAD) became higher than 50 points. The failure to effectively control the clinical condition of the patients by the use of routine therapeutic agents such as oral antihistamines, topical corticosteroids, topical moisturisers and topical calcineurin inhibitors were also considered in these patients.[10,17,18] Written informed consents were acquired from all patients or their legal guardian(s) and the process of this study was approved by the Ethics Committee of Tehran University of Medical Sciences.

Immunological evaluations

In the first visit, a three-page questionnaire, including demographic information and complete medical history was filled for every patient with severe AD. A full clinical examination was performed and laboratory tests, including complete blood cell count (CBC), serum immunoglobulin level (IgA, IgG, IgM and IgE) and lymphocyte CD markers measurement, were done as indicated. Further immunological tests were performed if needed in some cases. The diagnosis of PIDs was made using the standard criteria of the Expert Committee of International Union of Immunological Societies (IUIS) on Primary Immunodeficiencies.[2]

Statistical analysis

The data were analysed using the SPSS program version 16.0. For the evaluation of immunological data and CD markers, we used results of initial test at the time of diagnosis. Comparisons between groups were performed using Student's *t*-test for continuous data; Mann–Whitney *U*-test was used when the distribution was not normal for the selected variable. Chi-squared and Fisher's exact tests were performed between groups to compare clinical presentations as indicated. *P*-values < 0.05 were considered as statistically significant.

Results

Patients' characteristics

Seventy-seven individuals with a well-established diagnosis of severe AD completed all stages of this study, but two patients were excluded from the study due to the presence of secondary immunodeficiency (cystic fibrosis and human immunodeficiency virus infections). Finally, a total number of 75 severe AD patients (44 male and 31 female) were investigated for possible underlying PIDs.