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ORIGINAL ARTICLE

Clinical characteristics and outcomes of primary antibody deficiency: A 20-year follow-up study

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Background/Purpose: Primary antibody deficiency is the most common disorder among primary immunodeficiencies. Recurrent infection and chronic lung change often lead to mortality and morbidity.
Methods: This study focused on the clinical presentation, molecular diagnosis, and outcomes of primary antibody deficiency in Taiwan pediatric group. Medical records of patients with primary antibody deficiency during the period 1990–2010 were retrospectively reviewed in one medical center.
Results: Among the 34 patients evaluated, X-linked agammaglobulinemia (XLA) (29.4%) and common variable immunodeficiency diseases (CVIDs) (29.4%) were the most common disorders presented with respiratory and skin infections. Some genotype/phenotype discordance was found in one family. Patients with XLA, CVID, and hyper-IgM syndrome without complications had higher trough and initial IgG levels, and shorter delays in diagnosis. Patients with trough IgG levels >700 mg/dL had less occurrence of bronchiectasis.
Conclusion: These results summarized clinical manifestations of primary antibody deficiency in pediatric group in Taiwan. Clinicians should strive to shorten delays in diagnosis and maintain higher trough IgG levels to decrease subsequent mortality and morbidity.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Introduction

Primary immunodeficiencies are disorders resulting in increased susceptibility to uncommon pathogens, and recurrent and severe infections. Aside from infections, autoimmune diseases and malignancy might also be the associated disorders. The wide range of incidence, from 1/500 to 1/500,000, in the general population is due to a variety of subtypes that cause various symptoms.[1,2] Among the heterogeneous groups of primary immunodeficiencies, different incidence reports from different regions in the world show that antibody deficiencies are the most frequently diagnosed disorders, ranging from 50% to 70%.[3–5]

In general, selective immunoglobulin A (IgA) deficiency is the most frequent primary antibody deficiency but its clinical symptoms are obscure.[6] However, the incidence rate of selective immunoglobulin A (IgA) deficiency varies between Western and Eastern countries. For example, the prevalence of selective IgA deficiency is 1:223 to 1:1000 in the USA,[7] while it is about 1:3230 in China.[8] Selective IgA deficiency is more common in Caucasians. X-linked agammaglobulinemia (XLA) and common variable immunodeficiency diseases (CVIDs) are the two major groups wherein Ig replacement is used to prevent complications. Another group of antibody deficiencies, transient hypogammaglobulinemia of infancy (THI), is noted in children aged 1–2 years. The disease course is often benign as serum Ig levels increase with age. In Taiwan, one large cohort study has shown that primary antibody deficiency is the predominant group (36.3%) of primary immunodeficiency, and recurrent sinopulmonary infection is the most common presentation.[9]

Once primary antibody deficiency is diagnosed, intravenous immunoglobulin (IVIG) provides an effective treatment to improve survival and prevent infections,[10–13] with earlier institution of IVIG treatment providing better outcomes. Under regular IVIG replacement, the survival rate increases to more than 90%.[3,9] However, recurrent infections, bronchiectasis, and impaired lung functions are still major complications in spite of IVIG replacement, so many studies have focused on finding optimal serum IgG levels to prevent complications.

The current study focused on pediatric patients with primary antibody deficiency in a tertiary center and recorded initial Ig levels, trough IgG levels, diagnosed ages, initial presentations, and subsequent symptoms. The study also aimed at determining the relationship between Ig levels and outcomes.

Materials and methods

Data collection

The charts of the patients with suspected antibody deficiencies, indicated by the International Classification of Disease, Ninth Revision (ICD-9), in the Department of Pediatrics of National Taiwan University Hospital from 1990 to 2010 were screened and retrospectively reviewed. This study was approved by the institutional review board of National Taiwan University Hospital. The ICD-9 codes ranged from 279.00 to 279.09, which represented disorders of humoral immunity. Initially 232 patients were enrolled, and we excluded those who did not meet the criteria of the World Health Organization Scientific Group, the Pan-American Group for Immunodeficiency, and the European Society for Immunodeficiencies.[14,15] Other secondary immunodeficiencies such as protein-losing enteropathy, chromosome abnormalities, drug-induced immunodeficiency, and prematurity were also excluded.

We recorded ages of onset, which were defined as the age at which the first episode of invasive infection or chronic course of sinusitis and otitis media occurred. Ages of diagnosis were also recorded when the final diagnosis was made in our hospital after a series of workups were done. Diagnosis delay time was presented as the duration from the time of disease onset to the time of diagnosis. Initial and subsequent episodes of infections of each patient were also recorded. Bacteremia and central nervous system infection were confirmed by documented pathogens from blood and cerebrospinal fluid cultures. Bronchiectasis was diagnosed by chest radiography and computed tomography. Lung function tests were done by standard spirometry. Each documented pathogen of infection was presented to see the specific distribution.

Immunologic studies and molecular analysis

All patients received immunologic tests by standard techniques, including complete blood count with differential count, serum Ig levels, functional antibody levels, and lymphocyte subsets by flow cytometry. Mitogen tests for lymphocyte proliferation assay, CH50, neutrophil oxidative burst assay, and chemotaxis assay were performed in some patients to exclude other immunodeficiencies. Bruton tyrosine kinase (*BTK*) genes were analyzed by polymerase chain reaction-direct sequencing. CD40/CD40 ligand was analyzed by flow cytometry and genomic DNAs of two patients were sent to the Queen Mary Hospital in Hong Kong for CD40 ligand sequencing.

Outcomes

Patients with XLA, CVID, and hyper-immunoglobulin M (IgM) syndrome were further divided into the complication and the noncomplication groups based on the subsequent symptoms and outcomes during follow-up. The complication group included patients with chronic sinusitis, otitis media, pneumonia, invasive bacterial infections, bronchiectasis, impaired lung function, failure to thrive, malignancy, and autoimmune diseases, or those with mortality. Patients in the noncomplication group had no other morbidity or severe infections.

Statistical analysis

Data were expressed as mean $\pm$ standard deviation for age, laboratory data, and individual values with percentage for episodes of symptoms and infections. Data analysis was performed using the computer-based SPSS statistical software (version 17.0). Mann–Whitney *U* test was used to compare the diagnosis delay, age of onset, and initial and trough IgG levels in patients with and without long-term complications. Fisher's exact test was used to analyze the relationship between subsequent symptoms and trough IgG levels.