CLINICAL RESEARCH STUDY

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Adult Primary Immune Deficiency: What Are We Missing?

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ABSTRACT

BACKGROUND: More than 200 primary immune deficiencies have been described. In adults, their identification can be difficult. The lack of timely referrals, diagnostic facilities, and available expertise often delay appropriate treatment. Because an increasing number of adults are now diagnosed with immune deficiencies, there is a need to better understand the immune deficits in this age group. The study objective was to analyze the diagnostic spectrum of adults with primary immune deficiency and to determine the presumptive diagnostic accuracy of the referring physicians.

METHODS: We conducted a retrospective chart review over a 10-year period of all individuals referred to a dedicated center for adults with primary immune deficiency. Suspected cases were confirmed using standard clinical criteria and state of the art immune assays.

RESULTS: Of the 381 individuals studied, 244 were diagnosed as immune deficient. Of these, 210 had primary immune deficiency classified as novel, defined, and undefined. Forty-three patients had a prior diagnosis and were referred for follow-up care, and 201 patients were newly diagnosed. Most patients had common variable immune deficiency. Despite an apparent high index of suspicion in initiating the referrals, only one third of these patients had a prior quantitative assessment of serum immunoglobulins.

CONCLUSIONS: In this first known analysis of a large cohort of adults with suspected immune deficiency using established diagnostic criteria, we confirmed the diagnosis in two thirds of all patients. Our findings highlight the wide spectrum of primary immune deficiency states seen in adult medical practices and the need for increased awareness of their existence.

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Primary immune deficiencies are caused by inherited defects in the immune system. More than 100 molecular defects, predominantly in children, have been described recently.[1,2] An increasing number of adults are being diagnosed with primary immune deficiency, and recent studies estimate that up to 1:1200 people in the United States are diagnosed with some form of primary immune deficiency.[3] Immunoglobulin (Ig)-A, the most commonly diagnosed in the western world, is usually subclinical in presentation, with an incidence in Caucasians of up to 1:600.[4] The most frequently diagnosed adult primary immune deficiency with clinical importance is common variable immune deficiency, with a prevalence of 1:25,000 among Caucasians.[4] Usually, higher rates of primary immune deficiencies are observed in populations with high consanguinity rates or among genetically isolated populations.[1]

These deficiencies are a highly variable set of disorders with a diverse range of genotypes and clinical and immune phenotypes. In addition to the well-defined syndromes, subtle and often subclinical immune defects can occur in adults. These are expressed with variable penetrance and may go unrecognized in general clinical practice. Often, individuals are recognized as immune deficient after extensive investigations for unforeseen, unusual, recurrent, or severe infections. Because of the relative rarity, clinical heterogeneity,

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and limited diagnostic tools, misdiagnoses in clinical settings and misclassification of patients often occur. Delays in making specific diagnoses lead to late initiation of appropriate therapies and subsequent, often irreversible, complications.[5]

Abnormalities in humoral immunity account for more than 50% of primary immune deficiencies.[6] Individuals with these defects, among other problems, are susceptible to bacterial infections. T-cell anomalies account for fewer primary immune deficiencies but are considerably more severe and often fatal.[7] In adults, deaths may occur from opportunistic infections or neoplasms. Children may present with a failure to thrive.[7]

A majority of adults with primary immune deficiencies are not diagnosed or treated early in their course.[8] This is due to an overall paucity of prevailing knowledge of these illnesses in the health care community and to an insufficient awareness of the existence of such conditions in adults.

CLINICAL SIGNIFICANCE

- A high proportion of adults referred to us were confirmed to have an immune deficiency.
- Despite the high index of suspicion, screening immunoglobulin levels were carried out only in a minority of those referred.
- Current guidelines for the diagnosis of immune deficiency could not classify all our patients.
- Older individuals with a history of recurrent or severe infections may have a humoral immune deficiency characterized by low levels of B cells.

In 2000, the Immune Deficiency Treatment Centre of the McGill University Health Centre established a clinic dedicated to the diagnosis and care of adults with primary immune deficiencies. The aims of the clinic are to improve the long-term management of young adults with primary immune deficiencies transitioning to adult care; identify, diagnose, and manage adults with primary immune deficiencies; and raise awareness in the medical community of the existence of these adult disorders.

Our study objectives were to determine the spectrum of immune defects in this adult cohort and to determine the presumptive prereferral diagnostic accuracy of immune deficiency by the referring physicians.

MATERIALS AND METHODS

We conducted a retrospective chart review of all referrals to our center with a suspected diagnosis of immune deficiency during a 10-year period (January 1, 2000, to December 31, 2009). Established clinical and laboratory diagnostic criteria used to identify primary and secondary immune deficiencies were based on guidelines of the European Society for Immunodeficiencies and the Pan-American Group for Immunodeficiency (ESID/PAGID).[9] Immune testing included but was not limited to

- extensive immunophenotyping of T, B, and natural killer cells;
- lymphocyte functional assays, such as lymphocyte proliferative responses to mitogens and recall antigens, cytokine release assays, and in vivo anergy screening;
- macrophage function assays;
- quantitative serum complement and immunoglobulin isotype quantitation assays of specific antibody responses to a variety of vaccine challenges; and
- enzymatic and genetic assays as necessary. Institutional approval for the study was obtained from the McGill University Health Centre.

The study included adults (aged >18 years) at the initial evaluation, where the reasons for referral, clinical presentation, suspected pre- and final postevaluation diagnoses were available. Individuals with human immunodeficiency virus infection or receiving immunosuppressive therapy were excluded from the study.

Statistical Analysis

The Mann-Whitney test was used for comparing data sets that were non-normally distributed. For normally distributed data, the Student t test was used. P values $\leq .05$ were regarded as significant.

RESULTS

Patient Demographics

A total of 381 individuals met the study entry criteria. **Figure 1** outlines the diagnostic algorithm and classification by the presence and type of immune deficiency. **Table 1** lists the distribution of gender, age, and racial profiles for each group of referred patients.

The patients were almost exclusively Caucasian (97%), and the majority were female (61%). The median age did not differ by gender. The median age at the date of referral was 48 years in men and 45 years in women. Patients with primary and secondary immune deficiency did not differ significantly with respect to gender or ethnicity; however, men with secondary immune deficiency were older than those diagnosed with primary immune deficiency. Those with autoinflammatory and autoimmune syndromes were younger but did not differ in gender and ethnicity from those with immune deficiency.

Most referrals originated from medical subspecialists. The majority (55%) were from allergists and clinical immunologists, otorhinolaryngologists, and pulmonologists. Only 17% came from family practitioners and internists. A diagnosis of immune deficiency was confirmed in 244 individuals, representing 64% of the study patients (**Table 1**).

Clinical Phenotypes

Patients were grouped according to the presence or absence of immune deficiency on the basis of a combination