Beyond the apparent: Subtle presentation of immunodeficiencies in the age of personalized medicine

Chi-Chang Shieh a,b,*, Chih-Hsing Hung c,d

a Department of Pediatrics, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
b Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
c Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
d Department of Pediatrics, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan

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More than 6 decades have passed since the report of hypogammaglobulinemia, the first well-characterized primary immunodeficiency disease (PID), was published. However, clinicians and medical researchers are still constantly amazed by the new developments in this group of complex and often fatal diseases. With the rapid increase of knowledge in clinical immunology, new entities of PID arise with a fast pace. At the same time, deeper understanding of the immunodeficiency diseases continues to reveal key immunological facts. These novel discoveries from researches on patients with PID also facilitate the development of new clinical tools to benefit these patients with increased susceptibility to pathogenic microorganisms.

At least 176 hereditary entities have been described in this group of diseases and many of them are clinically apparent from an early age. Like most inheritable diseases, PIDs have been traditionally known as the devastating diseases caused by mutations on key functional proteins, which lead to total or nearly total loss of immune defense. However, more complex immunopathogenic mechanisms have been found to impede immune responses against specific microorganisms and lead to subtle or late-onset immunodeficiencies in otherwise "healthy" individuals.

Adult-onset immunodeficiency in Asia

A study by Browne et al on patients in Taiwan and Thailand recently revealed an example of a late-onset immunodeficiency more prevalent in people of Southeastern Asian origin. The HIV-negative adult patients in that study were found to have predisposition to infections by nontuberculous mycobacteria alone or with other opportunistic infections (e.g. fungi including Cryptococcus neoformans, Histoplasma capsulatum, Penicillium marneffei, and bacteria including Salmonella spp.). Although the patients had adequate CD4+ T lymphocytes (>350/μl) and the washed leukocytes had intact cytokine production in response to cytokine stimulation, their plasma inhibited in vitro IFN-γ detection and activity of IFN-γ on normal cells. High-titer anti-IFN-γ autoantibodies occurred in around 90% of the groups with disseminated NTM but in only 2% of the control groups. Although autoantibodies against proinflammatory cytokines including IFN-γ, IL-17A, IL-17F, and IL-22 have been reported previously and several case reports describing such patients have been published before, the recent study by Browne et al is the most

* Corresponding author. Institute of Clinical Medicine, National Cheng-Kung University, 138 Sheng-Li Road, Tainan 70403, Taiwan.
E-mail address: cshieh@mail.ncku.edu.tw (C.-C. Shieh).
systematic study on this immunodeficiency disease, presumably more prevalent in Southeast Asia, which is a region less intensively investigated regarding immunodeficiencies before.

**Approaches to pinpoint subtle leukocyte function defects with molecular diagnosis**

Early diagnosis of infection from both host and pathogen sides are crucial for successful treatment. However, the presentation of infections in patients with subtle immunodeficiencies may challenge the conventional wisdom of clinical diagnosis. As exemplified in a study published in this issue of JMI by Wang et al., the subtle initial clinical presentation in patients with nonoverwhelming immunodeficiency may be localized and prolonged in the course of their infections. However, without accurate diagnosis and timely treatment, the infection can become disseminated and debilitating. As reported by Wang et al, in these patients who have been denied a diagnosis for up to 10 years, measurement of cytokines, detection of leukocyte surface receptors and DNA sequencing of suspected genes were accomplished rapidly and led to the diagnosis of Mendelian susceptibility to mycobacterial diseases. Moreover, the development of array methods to detect disease-causing microorganisms enabled the clinicians to treat the patients effectively and in a timely manner. The successful molecular diagnoses in both host and pathogen sides highlight the feasibility of novel diagnostic methods in clinical care of PID patients. Given the recent increase in number of reports on molecular characterization of immune responses to difficult infections, we can reasonably expect that the detection of subtle immunodeficiency will become more common in the near future.

**PID: Under-reported and under-treated**

Although various forms of registry of PID have been ongoing for decades in the nations such as the United States, France, United Kingdom, Japan, and Taiwan, estimation of prevalence or incidence based on these registries have been in doubt since most of these registries have to rely on voluntary reporting of physicians. Based on a community-wide survey, a nationwide random telephone survey in the USA, and data from registries for PID, Bousfiha et al estimated the prevalence of PID may be 6 million worldwide, whereas only 27,000 (all national registries) to 60,000 (the Jeffrey Modell Centers Network) have been identified to date in registries. Even in Europe, only 2.27% of the patients are currently registered. Moreover, PID were prevalent not only in children, but also in adults. The registry rate of PID in adults, due the lower awareness of PID in adult physicians, was even lower. If their estimations are close to the truth, the prevalence and incidence of PIDs are similar to those observed for diseases such as leukemia.

The discrepancy between the estimated numbers of patients and those who are clinically registered might explain many reported unusual infections that may lead to treatment failure in presumably immune-competent patients. Considering the severe personal suffering and potential cost of treatment for difficult infections, diagnosis of non-HIV induced immunodeficiencies should be pursued diligently. Systematic and dedicated epidemiological studies on PID are therefore required to obtain essential information for clinically significant immunodeficiencies especially in Eastern Asian countries, which are less extensively explored regarding the occurrence of PID.

**Immunodeficiency in the age of personalized medicine**

By extending our understanding of the pathophysiology of immunodeficiency from phenomenology to cellular and subcellular mechanisms, we have increased our ability to manipulate the immune responses to the patients’ benefit. Development of diagnostic tools in regions other than United States and Europe has enabled us to identify PID rarely seen in the more developed countries. This will no doubt broaden the scope of the understanding on human PID and will prove to be crucial for the subtle modification for treatment for immune-relevant diseases in the new age of personalized medicine.

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