Journal of Microbiology, Immunology and Infection (2012) 45, 395–397

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.e-jmii.com

PERSPECTIVE

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

Received 11 August 2012; accepted 23 August 2012

More than 6 decades have passed since the report of hypogammaglobulinemia, the first well-characterized primary immunodeficiency disease (PID), was published.[1] 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.[2] 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.[3]

At least 176 hereditary entities have been described in this group of diseases and many of them are clinically apparent from an early age.[4] 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.[5] The HIV-negative adult patients in that study were found to have predisposition to infections by non-tuberculous 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 ($>350/\mu l$) 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.[5] Although autoantibodies against proinflammatory cytokines including IFN-γ, IL-17A, IL-17F, and IL-22 have been reported previously[6,7] and several case reports describing such patients have been published before,[8] the recent study by Browne et al[5] 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).

http://dx.doi.org/10.1016/j.jmii.2012.08.023

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 *JMII* 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.[9] 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,[10,11] 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,[12,13] 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.[14] 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.[14] 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.[9,15] 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.

Funding

CCS and CHH were supported by grants from the National Science Council and National Health Research Institute, Taiwan.

References

1. Bruton OC. Agammaglobulinemia. *Pediatrics* 1952;**9**:722—8.
2. Notarangelo LD. Primary immunodeficiencies. *J Allergy Clin Immunol* 2010;**125**:S182—94.
3. Maródi L, Casanova JL. Primary immunodeficiencies may reveal potential infectious diseases associated with immune-targeting mAb treatments. *J Allergy Clin Immunol* 2010;**126**:910—7.
4. Al-Herz W, Bousfiha A, Casanova JL, Chapel H, Conley ME, Cunningham-Rundles C, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Immunol* 2011;**2**:54.
5. Browne SK, Burbelo PD, Chetchotisakd P, Suputtamongkol Y, Kiertiburanakul S, Shaw PA, et al. Adult onset immunodeficiency in Thailand and Taiwan. *N Engl J Med* 2012;**367**:725—34.
6. Burbelo PD, Browne SK, Sampaio EP, Giaccone G, Zaman R, Kristosturyan E, et al. Anti-cytokine autoantibodies are associated with opportunistic infection in patients with thymic neoplasia. *Blood* 2010;**116**:4848—58.
7. Puel A, Döffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med* 2010;**207**:291—7.
8. Chen YP, Yen YS, Chen TY, Yen CL, Shieh CC, Chang KC. Systemic *Mycobacterium kansasii* infection mimicking peripheral T-cell lymphoma. *APMIS* 2008;**116**:850—8.
9. Wang LH, Yen CL, Chang TC, Liu CC, Shieh CC. Impact of molecular diagnosis on treating Mendelian susceptibility to mycobacterial diseases. *J Microbiol Immunol Infect* 2012;**45**, in this issue.
10. Liu YC, Shin-Jung LS, Chen YS, Tu HZ, Chen BC, Huang TS. Differential diagnosis of tuberculous and malignant pleurisy

using pleural fluid adenosine deaminase and interferon gamma in Taiwan. *J Microbiol Immunol Infect* 2011;**44**:88—94.
11. Tan CK, Lai CC, Lin SH, Huang YT, Liao CH, Hsueh PR. Diagnostic utility of enzyme-linked immunospot assay for interferon-gamma in a patient with tuberculous arthritis and pyomyositis. *J Microbiol Immunol Infect* 2011;**44**:397—400.
12. Ishimura M, Takada H, Doi T, Imai K, Sasahara Y, Kanegane H, et al. Nationwide survey of patients with primary immunodeficiency diseases in Japan. *J Clin Immunol* 2011;**31**:968—76.
13. Lee WI, Huang JL, Jaing TH, Shyur SD, Yang KD, Chien YH, et al. Distribution, clinical features and treatment in Taiwanese patients with symptomatic primary immunodeficiency diseases (PIDs) in a nationwide population-based study during 1985-2010. *Immunobiology* 2011;**216**:1286—94.
14. Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova JL, et al. Primary immunodeficiency diseases worldwide: more common than generally thought. *J Clin Immunol* 2012. Epub ahead of print.
15. Su SH, Tsai WC, Lin CY, Lin WR, Chen TC, Lu PL, et al. Clinical features and outcomes of spinal tuberculosis in southern Taiwan. 2010. *J Microbiol Immunol Infect* 2010;**43**: 291—300.