A Drop of Prevention is Worth a Liter of Cure: The Case for Newborn Screening for Severe T Cell Immune Deficiency in Israel

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Inherited primary immune deficiency diseases cause increased susceptibility to infections, autoimmunity and cancer. Major advances have been made in the treatment of PID through the use of immunoglobulin replacement, allogeneic hematopoietic stem cell transplantations, gene therapy, etc. However, delay in the diagnosis of PID often leads to increased morbidity and mortality [1]. Accordingly, in the last decade there have been attempts to develop tests to identify PID, particularly profound T and B cell immune deficiencies, as early in life as possible. Recently, assessment of T cell receptor excision circles has emerged as an accurate and cost-effective method for detecting severe T cell immune deficiency [2]. TREC are short segments of excised genomic DNA produced in thymocytes during rearrangement of genes encoding the T cell receptor [3]. TREC remain in T cells that emigrate from the thymus to the peripheral blood, thereby providing a relatively easy, albeit indirect, tool to assess the function of the thymus, the birthplace of T cells. Moreover, TREC are surrogates for T cells, therefore measurement of TREC avoids the cumbersome and expensive flow cytometry analysis commonly employed to determine the presence of T cells in peripheral blood. Importantly, the ability to extract genomic DNA from dried blood spots, such as those found on the well-established "Guthrie card" used since the 1960s for newborn screening, enables screening of large populations.

In 2008, Wisconsin was the first state in the U.S. to implement TREC screening for severe T cell immune deficiency in newborns, followed by Massachusetts, California, New York and others [4,5]. To date, 14 states have implemented screening for T cell immune deficiency, with 12 more expected to begin pilot studies or screening programs in the coming year, encompassing more than 50% of all newborns in the USA. Similarly, Ontario, the province with the largest number of births in Canada, will start newborn screening for severe T cell immune deficiency in 2013. Among the almost 1 million newborns screened across the USA, T cell defects were identified in 60 infants, or at about 1/16,600 live births [6], although not all suffered eventually from severe immune deficiency [7]. Similarly, a recent update from California reported the identification of 26 patients with T cell immune deficiency among 1.26 million newborns screened during the first 30 months [Puck, personal communication, May 2013]. While the precise prevalence of severe T cell immune deficiency in Israel is still unknown, it is likely even higher than in the USA because of increased consanguinity and "founder effect" in some communities.

In the present issue of *IMAJ*, Somech and co-authors report on the ability of TREC to identify PID in Israeli infants [8]. The authors, from three leading tertiary referral centers experienced in the diagnosis and management of PID in Israel, treated seven infants with severe T cell immune deficiency during a 1 year period. The median age at diagnosis of these patients was 7 months; many patients suffered from recurrent infections prior to the diagnosis. Importantly, Somech and team demonstrate that all seven patients had markedly reduced TREC in DNA extracted from Guthrie cards. Accordingly, these patients could have been diagnosed immediately after birth, which would have significantly reduced the patients' morbidity as well as expenses for the medical system.

Moreover, Somech et al. demonstrate that measuring kappa-deleting recombination excision circles from Guthrie cards can be used for assessing B cells and detection of profound B cell immune deficiency in infants [8]. Defects in the development of B cells with subsequent abnormal antibodies and immunoglobulin production are tenfold more common than T cell immune deficiency [1]. Hence, newborn screening for KREC, in addition to complementing detection of T cell immune abnormalities, has the potential to significantly impact the management of many more patients with PID.

Despite the high sensitivity and specificity of TREC newborn screening for severe T cell immune deficiency, there might be

PID = primary immune deficiency diseases
TREC = T cell receptor excision circles

KREC = kappa-deleting recombination excision circles

false-positive results, particularly among premature infants, causing unnecessary anxiety and investigations [4]. Also, for some patients identified by TREC newborn screening, such as those suffering from ataxia-telangiectasia, there might not be immediate management options [9]. Moreover, the newborn screening might not detect all patients with severe T cell immune abnormalities, such as X-linked hyper-IgM syndrome, partial adenosine deaminase deficiency and other PID [10, 11]. Thus, health care providers need to remain vigilant and consider PID even in those whose newborn screening was normal.

In conclusion, although some challenges remain, there is already overwhelming data, including the recent pilot study by Somech et al. [8], that newborn screening for severe T cell immune deficiency will save the lives of many Israeli children. Accordingly, the 2013 decision by the Israel Ministry of Health not to add TREC testing to its newborn screening program should be reconsidered.

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Capsule

Biological features of a novel avian influenza A (H7N9) virus

Human infection associated with a novel reassortant avian influenza H7N9 virus has recently been identified in China. A total of 132 confirmed cases and 39 deaths have been reported. Most patients presented with severe pneumonia and acute respiratory distress syndrome. Although the first epidemic has subsided, the presence of a natural reservoir and the disease severity highlight the need to evaluate its risk on human public health and to understand the possible pathogenesis mechanism. Zhou et al. show that the emerging H7N9 avian influenza virus poses a potentially high risk to humans. The authors discovered that the H7N9 virus can bind to both avian-type (α2,3-linked sialic acid) and human-type (α2,6-linked sialic acid) receptors. It can invade epithelial cells in the human lower respiratory tract and type II pneumonocytes in alveoli, and replicate efficiently in ex vivo lung and trachea explant culture and several mammalian cell lines. In acute serum samples of H7N9-infected patients, increased levels of the chemokines and cytokines IP-10, MIG, MIP-1β, MCP-1, IL-6, IL-8 and IFNα were detected. They note that the human population is naive to the H7N9 virus, and current seasonal vaccination could not provide protection.

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Capsule

Regulatory T cells protect the gut

Regulatory T cells (Tregs) in the gut are important sentinels in maintaining the peace between our gut and its trillions of resident bacteria and have been shown to be regulated by specific strains of bacteria in mouse models. Smith and collaborators question whether metabolite(s) generated by resident bacterial species may regulate Tregs in the gut. Indeed, short-chain fatty acids (SCFAs), bacterial fermentation products of dietary fibers produced by a range of bacteria, restored colonic Treg numbers in mice devoid of a gut microbiota and increased Treg numbers in colonized mice. The effects of SCFAs on Tregs were mediated through GPCR43, a receptor for SCFAs, which is expressed on colonic Tregs. Mice fed SCFAs were protected against experimentally induced colitis in a manner that was dependent on GPR43-expressing Tregs.

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