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 transplantsations, 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 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.

In the present issue of IMAJ, 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
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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References