Neugeborenenscreening für schwere angeborene Immundefekte

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Primary immunodeficiencies (PID) are congenital disorders of immune competence, which are mainly characterized by a pathological susceptibility to infection. This is often accompanied by severe recurrent infections with drug-resistant, long progressions. In addition, there are associated immune regulation disorders, which may manifest themselves in granuloma formation, auto-immunity, recurrent fever, eczema, lymphoproliferation and chronic intestinal inflammation. More than 240 disease entities have been defined so far as PID, and just as extensive is the spectrum of clinical severity. While the most common congenital immunodeficiencies, such as selective IgA deficiency or C2 complement deficiency, have a mild phenotype which often remains undetected, severe PID are characterized by significant mortality in the first years of life, as well as a serious morbidity with irreversible organ damage. This applies in particular to PID that are defined by the absence or functional anergy of T-lymphocytes (severe combined immunodeficiency; SCID) or B-lymphocytes (e.g. X-linked agammaglobulinemia; XLA). Patients with such severe congenital immunodeficiencies appear to be in perfect health at birth, yet show initial manifestations of SCID between the 14th day and the 4th month following birth; in patients with XLA usually between the 8th and 16th month after birth.

Albeit increasingly becoming appreciated as a relevant health problem, there is a lack of diagnostic procedures and screening profiles that would allow earliest possible diagnosis of patients with severe PID on a population scale. As a superior prognosis could be given upon prompt diagnosis and immediate adequate treatment, one strategy to improve the outcome of severe PID shall be to test newborns for the presence of T and B cells. With the aim to develop a simple and reliable test for newborn screening using the established dried blood sampling system (Guthrie cards), a multiplex real-time quantitative qPCR assay for the quantitation of T cell receptor excision circles (TRECs) and kappa-deleting recombination excision circles (KRECs) as surrogate markers of T and B cell development was designed and

evaluated. This assay was further extended to allow detection of newborns with an inversion of the *UNC13D* gene, causing a severe PID characterized as familial hemophagocytic lymphohistiocytosis. Furthermore, the feasibility to identify several other severe PID, characterized by a functional defect of T- and B-cell interation (combined immunodeficiency diseases), was assessed using IgA-protein detection in neonatal Guthrie cards. However, this assay provided evidence of a maternal transfer mechanism for IgA, thereby preventing the use of this assay as a screening tool for severe PID. Finally, the TREC-KREC newborn screening assay was further improved in terms of assay performance and evaluated in retrospective cohorts of patients with the DiGeorge syndrome, or Down syndrome. In addition, novel second-tier assays for comfirmation of the 22q11 microdeletion or the chromosome 21 triplication have been designed and succesfully tested with neonatal samples.

In summary, new assays and concepts for newborn screening of severe primary immunodeficeincies were designed and benchmarked in retrospective and prospective neonatal dried blood spot samples, thereby underlining the potential of this preventive health care strategy.