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EDITORIAL

Extending neonatal screening to the detection of severe combined immunodeficiencies. A moral imperative☆

Ampliación del cribado neonatal a la detección de inmunodeficiencias combinadas graves. Un imperativo moral

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It is estimated that every year between 5 and 10 children are born in Spain with severe combined immunodeficiency (SCID). Until the advent of haematopoietic stem cell transplantation (HSCT), all these patients died from serious infections. The possibility of HSCT with the higher rates of success the younger the patient is, and the recent appearance of a robust test[1] to diagnose them at birth, make SCID a prime candidate for implementation in neonatal screening in Spain.

Since their description by Wilson and Jungner in 1968, the criteria for including a disease in the neonatal screening programme have been applied up to the present virtually unchanged.[2] They indicate that illnesses for potential inclusion must fulfil the following principles: (a) the condition should be an important health problem by reason of its prevalence and/or burden of disease; (b) there should be a suitable screening test that is acceptable to the population; (c) the natural history of the condition should be thoroughly understood; (d) diagnostic, therapeutic or preventive measures should be available to offer to those affected; (e) treatment should be more effective in the latent phase than if it is applied after the usual clinical diagnosis, and (f) the cost of identifying cases should be economically balanced against the potential expenditure in overall medical care.

SCID represents in fact a set of genetically-determined diseases which groups together the most severe forms of primary immunodeficiency involving an almost complete failure of T-cell and/or B-cell lymphopoiesis. SCID definitely meets the criteria for inclusion in neonatal screening: it is a group of diseases with a prevalence of around 1:30,000–50,000 live neonates (according to actual results, not extrapolations, obtained in states of the United States of America that practise universal screening). This prevalence is far higher than that of most entities currently included in the extended screening programme carried out in various autonomous communities in Spain. SCID is a condition

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that is asymptomatic at birth but extremely serious, leading inevitably, in its classic forms, to death within the first 6 or 12 months of life. It should therefore be regarded as a medical emergency, given that early and optimised treatment is crucial to the patient's future. Early diagnosis has a major impact on the survival of the children affected. Thus recent studies have demonstrated that patients diagnosed in the absence of infections as a result of diagnosis of a sibling, have a much higher survival rate (90%) than those diagnosed on the basis of the natural history of the disease (40%).[3]

There is an early diagnostic technique that can be used for all the various genetic forms of SCID, known as T-cell Receptor Excision Circles (TRECs). Applied on dried blood spots in the newborn, it has recently emerged as a useful non-invasive tool for investigating the production of T-cells by the thymus. Quantification of TREC copies has been implemented as the preferred test to screen neonates with SCID or significant lymphopaenia.[1] Since it was first introduced as a pilot test in Wisconsin in 2007, the data provided in the various states where it is applied demonstrate its usefulness in the diagnosis and treatment of these patients, with a very low percentage of false positives and negatives. A further option for this screening is to supplement it with the evaluation of defects for defects in B lymphocyte development by adding the κ-deleting Recombination Excision Circles (KRECs) screening test, as proposed in various northern European countries; in any case, it would seem advisable to establish a single protocol (at least at the European level) that would make it possible to compare the results obtained.

Treatment of the various forms of SCID is based on HSCT and gene therapy in some specific cases, such as adenosine deaminase deficiency and interleukin-2 receptor gamma chain deficiency. Although gene therapy for these entities is not performed in Spain, there are paediatric hospitals available with extensive experience in the diagnosis and treatment of these diseases and therefore ready to provide follow-up and curative treatment for patients with SCID.[4]

From an economic point of view, the cost of TRECs and KRECs determination, performed by means of polymerase chain reaction (PCR) techniques, is theoretically higher, given that the current screening is done using a different technique, mass spectrometry. Nevertheless, available data on this subject demonstrate a very significant saving when comparing the overall care of these children in the presymptomatic phase with the normal management of a patient receiving care on the basis of the natural history of the disease, characterised by infectious complications that are typically severe and prolonged, requiring complex treatments which also make it more difficult to achieve a successful transplant. This factor provides further justification for routine screening from the point of view of efficiency.[5]

For all these reasons, a formal recommendation has been made by European experts that neonatal screening for SCID should be compulsory in all European countries.[6] Currently it is applied in 13 states of the USA (covering practically half the neonates in that country) and several countries are starting this process in Europe.

In this connection, the study carried out by Olbrich et al.[7] and published in this issue, entitled ''A first pilot study on the neonatal screening of primary immunodeficiencies in Spain: TRECs and KRECs identify severe T- and B-cell lymphopenia'', is relevant, groundbreaking (the first pilot study in Spain) and technically well executed. The authors assess the technical feasibility and that of the circuits involved, by quantifying two markers of lymphocyte replication (TRECs for T-lymphocytes and KRECs for B-lymphocytes) in dried blood spots from 1068 neonates. Their results, reinforced by their consistency in the use of internal controls of samples of patients with confirmed immunodeficiencies, show that both markers are useful in discriminating healthy children from those with SCID (which corroborates previous published studies in other populations), although they emphasise that two essential issues are still to be resolved: defining sensitive and specific cutoff points in the quantification of these PCRs and optimising the collection and storage of dried blood spot samples. A precise evaluation of the cost of this screening in our population, a crucial factor in determining its universal application, has yet to be made.

In short, SCID is a potentially fatal condition detectable by neonatal screening, which leads to a marked improvement in the prognosis of the children affected; moreover, such screening is cost-effective on the basis of preliminary data from other countries where it is being implemented. Consequently, it seems sensible to assert that neonatal screening for SCID ought to be a practical reality in the near future in this country, where budgetary limitations should make us prioritise all those actions that optimise our depleted health budgets by producing savings in the medium to long term, even if they involve short-term increases. In our view, Spain should not be behindhand in neonatal screening for SCID: such screening is sustainable and should be sustained over time.

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