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EDITORIAL

Fifty years of neonatal screening for congenital diseases in Spain☆

Cincuenta años de cribado neonatal de enfermedades congénitas en España

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Neonatal screening is a process aimed at the early detection of certain congenital diseases that may be asymptomatic but can cause severe mental or physical impairment and in which early diagnosis and treatment can significantly improve the prognosis.

The worldwide origins of neonatal screening date back to the 1960s, when Robert Guthrie and Ada Susi developed a bacteriological blood test for detection of elevated levels of phenylalanine through a simple, quick and reliable method with collection of a few blood drops left to dry in special filter paper. In Spain, the first neonatal screening programme targeted phenylketonuria and started in 1968, led by Professors Federico Mayor Zaragoza and Magdalena Ugarte from the Universidad de Granada. In the 1970s, screening was expanded to include detection of congenital hypothyroidism. In 1978, the Spanish Ministry of Health officially established the Programme for the Early Detection in Newborns of Phenylketonuria and Congenital Hypothyroidism (Royal Decree 2176/1978 of August 25).

At first, this screening programme was commonly referred to by the popular lay terms ''heel-prick test'' or ''endocrine-metabolic newborn screen'' in reference to phenylketonuria and congenital hypothyroidism, but these labels have since become insufficient, as early detection of some congenital blood disorders, immune disorders and hearing loss is now a reality in many regions and countries. Thus, some facilities gradually started introducing screening for other disorders such as congenital adrenal hyperplasia or biotinidase deficiency, and in the 1990s, the work of researchers in Duke University in the United States promoted the development of expanded screening programmes through the application of new technologies, such as tandem mass spectrometry (MS/MS), to analyse various metabolites, mainly acylcarnitines and amino acids that could serve as markers, in the dried blood spot samples that were already being collected.[1] This development has made possible the detection of over 40 different genetic disorders in a single dried blood spot sample from a newborn. In Spain, expanded screening was first introduced in Galicia in July 2000, with other autonomous communities gradually following suit. Aware of this breakthrough, the Interterritorial Council of the National Health System of Spain approved, in July 2013, and subsequently published in October 21, 2014 in the *Boletín Oficial del Estado* (Official State Gazette) Order SSI/2065/2014, which expanded the diseases included in the nationwide basic neonatal screening programme of the National Health System, recommending that it include 7 disorders: congenital hypothyroidism, phenylketonuria, cystic fibrosis, medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD), long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD), glutaric acidaemia type I (GA-I) and sickle-cell anaemia. Generally, these screening programmes are based on the analysis of blood samples

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collected on pieces of absorbent filter paper commonly referred to as ''Guthrie cards'' that must meet the criteria of the National Committee for Clinical Laboratory Standards. In this dried blood spot screen, so-called ''second-tier'' marker tests are very important. It is also possible to perform screening in urine samples by means of MS/MS, which allows confirmation of the diagnosis made based on initial samples, supplements the information obtained from the blood sample and opens up new diagnostic possibilities.[2] In Spain, neonatal screening includes analysis of both blood and urine samples in 3 autonomous communities (Galicia, Murcia and Extremadura).

The current issue of *Anales de Pediatría* includes 2 protocols for the diagnosis and follow-up of patients with 2 diseases for which neonatal screening is recommended in Spain and most countries in Europe and America: congenital hypothyroidism and cystic fibrosis.[3,4] Both works highlight the benefits of neonatal screening for these disorders, despite the lack of standardisation in testing methods. In Spain, screening for congenital hypothyroidism consists of measurement of thyroid stimulating hormone (TSH) levels in all autonomous communities but 3 (Basque Country, Navarre and Cantabria) where, as is the case of the United States, initial screening also includes measurement of thyroxine (T4) levels. Screening for cystic fibrosis is even more heterogeneous, with 3 possible strategies employed both in Spain and in other countries: measurement of immunoreactive trypsinogen (IRT) twice, measurement of IRT and DNA testing, or an IRT + IRT + DNA protocol.

Expanding current screening programmes poses challenges. In 1975, the Scientific Group on Screening for Inborn Errors of Metabolism of the World Health Organization proposed a set of criteria that disorders had to meet to be included in neonatal screening protocols based on the already classic principles established by Wilson and Jungner, but these criteria are no longer valid under current circumstances. Advances in diagnosis and treatment, ethical principles, long-term cost–benefit analysis, the positive impact on child and family welfare and the knowledge of the natural history of disease and the prevention of secondary health problems make these criteria subject to ongoing revision and result in significant variability and even contradiction in the approaches to screening.[5] As a result, there is considerable heterogeneity in the newborn screening programmes currently implemented worldwide, including those used in Spain. Several pilot studies are currently underway,[6] and the expansion of screening to include other diseases is being considered, with a tendency towards changing the original scheme by increasing the number of disorders to screen for, mostly inherited metabolic disorders (aminoacidopathies, organic acidaemias and cerebral acidosis, fatty acid oxidation defects, and in some centres, disorders of carbohydrate metabolism and some lysosomal storage disorders), but also endocrine disorders (congenital hypothyroidism, adrenal hyperplasia), blood disorders (sickle cell anaemia), respiratory-gastrointestinal disorders (cystic fibrosis), immune disorders (severe combined immunodeficiency), cardiovascular disorders (screening for congenital heart defects) and hearing loss.[7]

The development of new treatments for diseases that were untreatable to date or until recently and the introduction of emerging technologies applicable to new biochemical markers and massive DNA sequencing analysis may have a positive impact in the screening of congenital diseases in the future. Spain cannot lag in this progress in neonatal screening, which has been proven efficacious, efficient and effective, and which offers clear benefits to patients, whose prognosis and quality of life improve with early diagnosis and treatment.

Thus, today, with the perspective of 50 years of experience, we can assert that neonatal screening programmes are among the most significant advances that have taken place in public health, with nearly 400 000 children in Spain benefiting from them each year. Their universal implementation with a coverage of nearly 100% of newborns, despite screening not being legally mandated in Spain, has been one of the greatest achievements in paediatric clinical practice.

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