

## CLINICAL EFFECTIVENESS OF NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY

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**Introducción:** neonatal screening programmes are designed for the pre-symptomatic identification and early treatment of treatable congenital diseases, in order to reduce the morbidity and mortality and possible associated disabilities. These programmes have to guarantee equal, universal access for all newborns from the target population, providing correct information to parents to help in the decision-making process. However, neonatal screening should not be commenced if the benefits of their early detection are not clearly defined, and if there are no guarantees for the correct diagnosis, monitoring, and treatment for all children in which the disease is detected by the healthcare system.

**Objectives:** to evaluate the clinical effectiveness of neonatal screening for severe combined immunodeficiency (SCID) by quantifying T-cell receptor excision circles (TRECs) by PCR (qPCR).

**Methods:** a systematic review of the literature from the main biomedical databases, including Medline, Embase, Cochrane Library, HTA, DARE, and INAHTA. Two search criteria were used, one focusing on epidemiology, natural history, morbidity, mortality, diagnosis, and treatment without any time limit, and another focusing on screening for the disease. In order to obtain all of the relevant information, the process was completed with a manual review of the bibliography of the included articles, as well as a general internet search of official websites for screening programmes, organisations, and/or scientific associations. After reading the titles and abstracts of the articles that resulted from the search, a series of studies were selected based on previously established inclusion and exclusions criteria.

**Results and Discussion:** a total of 9 studies on screening programmes were included, all of which were prospective and observational. The quality of these studies was evaluated using the QUADAS-2 tool for diagnostic validity studies, generally obtaining a low bias risk and high applicability. SCID covers a heterogeneous group of congenital diseases which includes the most serious types of primary immunodeficiencies, which if left untreated generally lead to death in the first year of life.

### **Severe Combined Immunodeficiency (IDCG):**

SCID is characterised by a series of congenital defects of the immune system that affect the body's cellular and humoral immunity. These are genetic diseases of a mainly autosomal recessive pedigree, although the most frequent (45%) is X-linked, and caused by mutation in more than 30

different known genes. It is estimated that the worldwide incidence is 1:51,000 births, although there are racial and geographical variations. All of the patients are characterised by an absence of functional T-cells, which causes severe T-cell lymphopenia. The body loses the ability to eliminate or fight infections, meaning it becomes highly susceptible. They are classified according to the immunological phenotype in SCID, as T-cell negative and B-cell positive (T-B<sup>+</sup>), or SCID where both are missing (T-B<sup>-</sup>). Both groups include different types, with or without natural killer (NK) cells. SCID is asymptomatic during the first months of life, until the maternal antibodies disappear that provide a certain degree of immunity. The majority of the phenotypes do not present distinctive clinical symptoms, with patients presenting similar symptoms to those characterised by recurrent and persistent serious infections (meningitis, pneumonia, and sepsis), otitis media and chronic diarrhoea leading to significant weight loss, malnutrition, and delayed or deficient development. SCIDs have a high morbidity-mortality rate, with untreated patients generally dying in the first year of life. The screening test consists of obtaining and analysing a blood sample from the heel. Obtaining this sample is a safe and easy process, while the analytical process is more complex, and calls for refining the methodology and defining a screening protocol and algorithm (cut-off points, premature cases, etc.) which will condition the sensitivity and specificity of the test. Screening for SCID is based on quantifying the T-cell receptor excision circles in dry blood spots, using quantitative PCR techniques (qPCR). The differential diagnosis includes several syndromes with variable T-cell deficiencies (such as ataxia-telangiectasia, trisomy 18 or 21, CLOVES syndrome, or DiGeorge syndrome, amongst others); secondary T lymphopenias (such as congenital heart or gastrointestinal malformation, neonatal leukemia); idiopathic T lymphopenias (reduced T-cell count without genetic defect), as well as premature births. To confirm the diagnosis, a complete hemogram is carried out, together with flow cytometry to count T-cells in blood, and a genetic analysis. The aim of the treatment is focused on preventing infections, and restoring immunological function. The first preventive measures include isolating the patient, prophylactic treatment (with antibiotics, antiviral and/or antifungal drugs), and or replacement with immunoglobulins, as well as avoiding the use of vaccines with living microorganisms. The only curative option is allogenic hematopoietic cell transplantation (HCT). Other alternatives are gene therapy (for ADA deficiency and common x-linked gamma deficiency) and enzyme replacement therapy with ADA deficiency. The prognosis for patients is good, especially if the TPH is carried out at an early stage and the child is asymptomatic. A 5-year survival rate of 94% is indicated when it is carried out before 4 months of age, and if there is no prior history of infection. In the long term, some patients may present a variable degree of cognitive and behaviour effects, greater difficulty

in concentrating, attention, and hyperactivity, lack of development, endocrine alterations, or neurological problems. The sensitivity and NPV were close to 100% in all of the studies that provided the necessary data, apart from in 1, due to obtaining 1 FN result. The specificity was close to 100%, and the estimated VPP was close to 5%, although this was highly variable, due to obtaining FP.

### Conclusions:

- The evidence on the effectiveness of neonatal SCID screening programmes evaluated in this review is of a low methodological quality, and is based on observational studies, and occasionally on pilot programmes.
- Severe Combined Immunodeficiency has a sufficient latency period in order for the screening programme to achieve the expected benefit. Also, it has effective treatment, which is more effective in the latency phase than in the symptomatic phase. However, the screening test has a low PPV.
- Before setting up a screening programme, it is necessary to define a suitable screening protocol that optimises the sensitivity and specificity of the test, which details, amongst other aspects, the cut-off points for each population and laboratory.
- Finally, it is necessary to set up a series of information systems based on relevant and reliable pertinent results, which make it possible to evaluate whether the activities or procedures carried out as a part of a screening programme are adapted to the health requirements, both from the perspective of the population and the healthcare system. This information will help in the process of measuring whether the objectives have been met, for defining priorities, and in the decision-making process.