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Review: Why screen for severe combined immunodeficiency disease?

Short title: Why screen for SCID?

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Abstract

Newborn screening for severe combined immunodeficiency (SCID) is now routinely performed in many countries across Europe and around the world.

The number of T-cell receptor excision circles (TRECs) reflects T cell levels. TREC quantification is possible using dried blood spot (DBS) samples already collected from newborns to screen for other conditions. This method is very sensitive and highly specific.

Data in the literature show that the survival rate for children with SCID is much higher when the disease is detected through early screening, as opposed to a later diagnosis. Newborns diagnosed with SCID may receive the appropriate care quickly, before the onset of serious infectious complications, which raises survival rates, improves quality of life, and limits side effects and treatment costs.

At the request of the French Ministry of Health, France's National Authority for Health (*Haute Autorité de Santé*) is expected to issue recommendations on this topic soon. The nationwide DEPISTREC study, involving 48 maternity units across France, showed that routine SCID screening is feasible and effective. Such screening offers the additional benefit of also diagnosing non-SCID lymphopenia within the infant population.

Keywords

neonatal screening, newborn screening, severe combined immunodeficiency, severe lymphopenias, TREC, rare diseases, primary immunodeficiencies

Conflicts of interest

None.

1 Introduction

Severe combined immunodeficiencies (SCID) encompasses a group of heterogeneous genetic disorders characterized by greatly weakened cellular and humoral immunity.

SCID is a pediatric diagnosis and therapeutic emergency, infants are asymptomatic at birth, but die of infections during their first year if not diagnosed and appropriately treated. Most patients exhibit substantial T cell lymphopenia. B cells, if present, are not functional due to a lack of interaction with T cells. The disease incidence is estimated at 1:50,000 to 1:100,000 births. This may be an underestimate because some children may die from infections before SCID is diagnosed [1].

If not detected through neonatal screening, SCID patients develop severe early-onset infections that may have serious sequelae and limit the efficacy of curative treatments.

2 Clinical presentation

Results of neonatal physical examinations are normal for the majority of children with SCID. For those with family histories of SCID—less than 10% of this population—immunologic testing is performed at birth. Between the ages of 3 and 6 months, patients generally develop severe RSV (bronchiolitis), rotavirus (diarrhea), CMV, bacterial, or opportunistic fungal (e.g., *Pneumocystis*) infections. Failure to thrive, poor general status, and chronic diarrhea may soon complete the clinical profile. Erythroderma—secondary to maternal alloreactive T cells (maternofetal graft-versus-host disease) or due to autoreactive T cells (Omenn syndrome)—may be observed as early as the time of birth.

Most children with SCID exhibit neonatal lymphopenia. It is important to recall that lymphocyte levels below 2,500/mm³ at birth, or below 4,000/mm³ at 6 months, are abnormal and require investigation. Diagnosis may be supported by a chest X-ray (abnormal absence of thymic shadow) and lymphocyte subset analysis (CD3⁺<1,500/mm³ indicates severe T-cell lymphopenia).

Live vaccines (such as BCG, rotavirus, chicken pox, and MMR vaccines) are contraindicated because of the risk of generalized vaccinal disease. Blood products must be CMV-negative and leukoreduced. Breastfeeding is contraindicated if the mother is CMV-positive, as the virus may be transmitted through breast milk.

Children must be placed in protected areas to limit the risk of infections. Specific care should be provided by teams specialized in pediatric immunology, in order to initiate curative treatment (allogenic stem cell transplantation; enzyme replacement therapy, for adenosine deaminase deficiency; or gene therapy in selected cases).

SCID requires urgent medical attention. If not treated, children with the disease usually die in their first year.

Age at the time of transplantation and history of infections are the main predictors of a successful bone marrow allograft. In an article published in 2014, Pai et al. studied outcomes for 240 infant SCID patients who received allografts at 25 North American centers over a decade. They showed that the survival rate is higher when children receive transplantations before the age of 3.5 months and are not infected at the time of the hematopoietic stem cell transplantation [2].

3 Genetic diagnosis

SCID covers a range of genetic anomalies, and its variants are classified according to the presence or absence of T, B, and natural killer cells. Over the past two decades, molecular analysis has identified over a dozen genes linked to SCID. The associated autosomal recessive and X-linked genetic defects are summarized in Table 1 [3].

4 Neonatal screening

4.1 France far behind other European countries

Neonatal screening allows for the delivery of effective care that can change the course of the disease before the development of irreversible lesions. The collection of dried blood spot (DBS) samples—a few drops of blood on filter paper—3 days after birth enabled the development of neonatal screening in industrialized nations. Introduced first in the United States and later in Europe (1970), for phenylketonuria, DBS-based screening is currently used to detect a large number of other diseases. In 1968, the World Health Organization published guidelines for mass screening, known as the Wilson and Jungner criteria [4]. The number of diseases covered by screening would gradually rise thereafter. Until 2019, neonatal screening in France covered phenylketonuria, congenital hypothyroidism, congenital adrenal hyperplasia, cystic fibrosis, sickle cell anemia, and starting in 2012, deafness. Screening for medium-chain acyl-CoA dehydrogenase deficiency by mass spectrometry, recommended by the National Health Authority since 2011, will become routine in 2020.

Screening practices vary widely in Europe [5]. An analysis of national practices shows that neonatal screening ranges from 2 to 29 diseases, depending on the country, with no correlation with economic level (Table 2).

4.2 Neonatal screening for SCID and T-cell severe lymphopenias

SCID, although rare, fulfills major criteria for neonatal screening: It is a serious illness, it is asymptomatic at birth, it is easy to diagnose, and a curative treatment exists. In 2005, Chan and Puck developed a method for SCID screening that relies on quantification of T-cell receptor excision circles (TRECs) in DBS samples using PCR. [6] TRECs are DNA sequences removed upon TCR $\alpha\beta$ rearrangement, during T-cell maturation. Hence, TREC counts reflect the thymic output of mature T cells. TRECs are detected in naïve T cells and are not found in B or memory T cells. Tallying TRECs in peripheral blood lymphocytes is thus a good way to quantify recent thymic emigrants: Thymopoiesis increases TREC levels, while peripheral expansion or lack of thymopoiesis lowers them.

The Clinical Laboratory Standards Institute has issued recommendations for neonatal SCID screening, identifying forms of neonatal lymphopenia that result in failure to detect TRECs (Table 3) [7]. Wisconsin and Massachusetts were the first US states to adopt routine neonatal screening for SCID.

In 2010, the US Department of Health and Human Services issued its own recommendations regarding routine SCID screening in the United States. The practice has slowly spread there since then, and Canada, Israel, Taiwan, Hong Kong, Iceland, and New Zealand have followed suit.

In Europe, neonatal screening for severe lymphopenia based on TREC analysis is now routine in Germany, Sweden, Norway, Switzerland, and Denmark. There are also pilot studies or regional screening programs in Belgium, The Netherlands, Austria, France, Spain, [8] Italy, and the United Kingdom [8].

A team in Sweden has implemented a single screening technique via PCR quantification of TRECs and κ -deleting recombination excision circles that makes it possible to detect severe T- as well as B-cell lymphopenias via PCR quantification of TRECs and κ -deleting recombination excision circles. It detects not only SCID but also severe agammaglobulinemias and severe hypogammaglobulinemias [9]. The technique is now used in some countries regionally or nationwide.

5 DEPISTREC study findings

In 2013, Nantes University Hospital (CHU de Nantes) received a grant to run a health-economic research program (PRME: *Programme de Recherche Médico-Economique*), the DEPISTREC study, whose aim was to assess the feasibility, clinical utility, and cost-effectiveness of routine neonatal screening in France. It included nearly 200,000 newborns over a 2-year period. The experimental group of infants subject to neonatal screening was compared with a control group of children diagnosed with SCID, without screening, during the same period.

The DEPISTREC screening study identified three children with SCID, which corresponds to an incidence of 1 out of 63,500 live births. This rate is comparable to what has been reported in the literature since (and as a result of) the advent of screening. We also identified 59 newborns with non-SCID T-cell lymphopenia in the screening group. Among them, two had completely asymptomatic DiGeorge syndrome; three, combined immunodeficiencies (one compound heterozygous RAG1 deficiency [leaky SCID], one *TTC7A* mutation, and one heterozygous ADA deficiency), and one ATM. The infant with RAG1 deficiency underwent

successful transplantation at 18 months, before complications related to his pathology. Interestingly, a severe lymphopenia was also detected in a child whose mother received azathioprine for an inflammatory disease of the gastrointestinal tract during pregnancy [10,11].

In the control group, 28 SCID patients were included. The retrospective analysis of 21 neonatal DBS samples from these SCID patients showed positive TREC screening results, confirming that SCID diagnosis at birth would have been possible through screening. Furthermore, five children from this group died with severe infections due to SCID before they could receive transplants. It is very likely that diagnosis via neonatal TREC analysis could have prevented these deaths. This large-scale study demonstrated that routine SCID screening is both feasible and effective and offers the added benefit of permitting a diagnosis of non-SCID lymphopenia to be made [11, 12]. In light of this study, for technical and economic reasons (the cost of diagnosis per newborn varied with the volume of laboratory work), we recommend carrying out the tests in a limited number of laboratories.

6 Health-economic analysis

Health-economic analysis of data from the DEPISTREC study made it possible to calculate the cost of testing. However, it did not permit confirmation of the benefit, in terms of average cost, of earlier transplantation because of the very small number of children in the experimental group diagnosed with SCID (three babies, one of whom died). The test is relatively cheap. Its cost is estimated at \$4.22 in the United States [13] (\$4.22 in the study by

Chan et al. [14]) and €3.70 by the DEPISTREC study. Given the rareness of SCID and the cost of care for SCID patients, health-economic studies are needed to encourage health authorities to adopt routine screening for the disease.

In 2011, Chan and colleagues used a Markov model to evaluate the cost-effectiveness of universal neonatal screening for enhancing both the quality of life and the life expectancy of sick children, considering a study population drawn from five US states [15]. Their aim was to study whether the benefit of an early SCID screening program exceeds its cost when accounting for both actual life years and quality-adjusted life years (QALYs), which are measures of the economic value of human life. Global cost estimates (with and without screening) accounted for estimated mean costs associated with screening per se (equipment, laboratory work, and reagents), follow-up testing for confirmation (CBC and immunophenotyping), transplantation (whether early or late), medical appointments, hospitalization, immunoglobulin, transportation, and parents' lost working days. Utility value is expressed in QALYs, where 1 QALY is defined as a year of life spent in perfect health. Hematopoietic stem cell transplantation for SCID is estimated to offer 0.91 QALY per actual life year following the intervention. The annual global cost of SCID screening in the United States has been estimated at \$22,377,379 for a cohort of 4,112,052 newborns (2003 figure)—i.e., the additional cost of screening is \$5.44 per infant. Over a 70-year period, screening can add a total of 880 life years, or 802 QALYs, to the cumulative lifespan of the population studied by Chan et al. Thus, its cost-effectiveness (annual global cost of screening divided by gained life years or QALYs) is evaluated at \$25,429 per year of life or \$27,907 per QALY.

These figures represent additional costs in the case of early transplantation (i.e., after neonatal screening) with respect to late transplantation. To conclude, with an estimated cost of \$4.22 per child, neonatal SCID screening would likely be a cost-effective means of enhancing the quality and lengthening the duration of affected children's lives.

More recently, Yao Ding and colleagues conducted a health-economic study to evaluate the cost-effectiveness and net benefit of neonatal SCID screening via TREC assays using DBS samples in Washington State [15]. Their work was based on a cohort of 86,600 annual births and relied on published data and experts' evaluations for the following variables: incidence of SCID and non-SCID lymphopenias; the proportion of asymptomatic children who are detected through family history alone; test characteristics (sensitivity and specificity); and the costs of screening, diagnosis, and treatment. Ding et al. performed both cost-effectiveness (considering number of saved life years) and cost-benefit (considering the monetary value of averted deaths) analyses. They reported an estimated annual net screening cost of \$424,470, which is the difference between the estimated gross annual screening costs (\$741,376) and savings on treatment as a result of screening (\$316,905). Furthermore, 12.02 life years would be saved; thus, the estimated price of a saved life year is \$35,311. The authors used two different values of statistical life (VSLs): \$4.2 million (conservative estimate) and \$9 million. They calculated benefit-cost ratios of 2.71 (for VSL of \$4.2 million, with annual net benefit of \$1.26 million) and 5.31 (for VSL of \$9 million, with annual net benefit of \$3.19 million), arguing persuasively for universal SCID screening. Their model

therefore suggests that SCID screening in Washington State would probably be cost-effective and offer a net economic benefit.

7 Special considerations for TREC screening in preterm infants

Multiple studies have shown that TREC values for preterm infants are significantly lower than for full-term newborns, resulting in higher rates of false positive results for the former. During the DEPISTREC study in France, which ran from December 2014 to February 2017, TREC analyses were performed for a population of 196,517 newborns, including 16,276 preterm infants [11,12]. The overall recall rate (i.e., for either a second DBS sample or a doctor's appointment) was significantly higher ($p < 0.0001$) for preterm infants (1.36%) than for those born at term (0.12%). The rate of recall for an appointment alone was also significantly higher ($p < 0.0001$) for preterm infants (0.23%) than for those born at term (0.073%). Furthermore, analysis of gestational-age subgroups revealed that extremely preterm (born at <28 weeks of amenorrhea) and very preterm (born from 28 weeks to 32 weeks and 6 days of amenorrhea) infants specifically were recalled for an appointment significantly more often ($p < 0.001$) than full-term infants.

Among premature infants, overall recall rates (for either a second DBS sample or an appointment) and second-DBS recall rates for each gestational-age subgroup were always significantly higher than for the consecutive older subgroup. In other words, the younger the gestational age, the higher the recall rate. For example, the overall recall rate for the "extremely preterm" subgroup was 8.2% versus 2.76% for the "very preterm" subgroup ($p < 0.001$). Table 4 presents the significance of recall rate differences between gestational age

groups, considered in pairs. TREC levels (in copies/ μ L) decrease significantly as the length of term shortens: Median values were 114 for full-term infants, 98 for moderately preterm infants, 79 for very preterm infants, and 60 for extremely preterm infants ($p < 0.001$).

In light of the literature and our study's findings, we suggest the following protocol for screening of preterm infants: DBS samples should be collected during the first days of life (usually at around 72 h)—regardless of gestational age—so that newborns may be quickly treated if TRECs are not detected. If the first DBS sample is positive, but TREC levels are above the chosen cutoff value, a second sample should be collected near term (i.e., at around 37 weeks of gestational age). This delay in second DBS sample collection maximizes the chance of eliminating false positives but is short enough to avoid losing sight of the child, as preterm infants may still be hospitalized. If results are also abnormal for the second DBS sample, a lymphocyte subset analysis must be performed and an appointment scheduled with a primary care pediatrician.

8 Diagnostic approach for severe lymphopenia

When abnormal TREC levels are detected and confirmed through screening, a diagnostic procedure may be conducted to precisely identify the cause of lymphopenia. An appointment with the local primary care pediatrician must be organized as soon as possible for diagnosis evaluation. A careful history and physical examination are necessary, and additional analyses are done: blood count, lymphocytes population analysis. If the suspicion of SCID is confirmed, molecular DNA analyses are performed to identify the genetic abnormality.

The procedure is the same as that for children identified without screening, and conforms to what is recommended by the French DIP reference center (CEREDIH). The immediate concern is to identify patients with SCID who will need protective measures and immune system reconstitution therapy. TREC screening also identifies infants with a range of non-SCID disorders in which T-cell lymphopenia is sometimes severe: congenital syndromes (e.g., DiGeorge syndrome, trisomy 21, ataxia-telangiectasia), congenital heart diseases, congenital syndromes, maternal immunosuppressive medication treatment.

9 Conclusion

Neonatal screening for severe T-cell lymphopenias will transform immunologic practice through diagnosis at a presymptomatic stage. When abnormal TREC levels are detected through screening, a fast, thorough diagnostic procedure may be conducted to precisely identify the cause of the lymphopenia and then apply the appropriate therapeutic measures. The DEPISTREC study demonstrated the feasibility of screening in France.

Monitoring of the SCID screening process in France, conducted through the newly organized regional neonatal screening centers, should confirm its health-economic value.

The French Ministry of Health has asked the National Authority for Health to issue screening recommendations, which are expected to be available in 2021 and would be followed by a ministerial decision within months.

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Abbreviations

DBS	dried blood spot
QALY	quality-adjusted life year
TREC	T-cell receptor excision circle

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Tables

Table 1. SCID classification [3]

	Disease	Genetic defect	Inheritance
T-B⁻ SCID	RAG1 deficiency	<i>RAG1</i>	AR ^a
	RAG2 deficiency	<i>RAG2</i>	AR
	DCLRE1C (Artemis) deficiency	<i>DCLRE1C</i>	AR
	DNA PKcs deficiency	<i>PRKDC</i>	AR
	Cernunnos/XLF deficiency	<i>NHEJ1</i>	AR
	DNA ligase IV deficiency	<i>LIG4</i>	AR
	Reticular dysgenesis	<i>AK2</i>	AR
	Adenosine deaminase deficiency	<i>ADA</i>	AR
T-B⁺ SCID	γ c deficiency	<i>IL2RG</i>	XL ^b
	JAK3 deficiency	<i>JAK3</i>	AR
	IL7R α deficiency	<i>IL7R</i>	AR
	CD45 deficiency	<i>PTPRC</i>	AR
	CD3 δ deficiency	<i>CD3D</i>	AR
	CD3 ϵ deficiency	<i>CD3E</i>	AR
	CD3 ζ deficiency	<i>CD247</i>	AR
	Coronin-1A deficiency	<i>CORO1A</i>	AR
LAT deficiency	<i>LAT</i>	AR	

^aAR: autosomal recessive. ^bXL: X-linked.

SCID: severe combined immunodeficiency.

Table 2. Neonatal screening in Europe

Country	Number of disorders covered	SCID coverage
Austria	29	P ^a
Belgium	Wallonia: 7; Flanders: 11	P
Bulgaria	3	N ^b
Croatia	2	N
Cyprus	2	N
Czech Republic	12	N
Denmark	15	Y ^c
Estonia	2	N
Finland	1	N
France	6 (+ deafness)	P
Germany	15	Y
Greece	3	N
Hungary	25	N
Ireland	5	N
Italy	2	P
Latvia	2	N
Lithuania	2	N
Luxembourg	4	N
Malta	3	N
Netherlands	20	Y (pilot)
Poland	3	N
Portugal	25	N
Romania	2	N
Slovakia	4	N
Slovenia	2	N
Spain	27	P (Catalonia)
Sweden	5	Y
United Kingdom	7	N

^aP = partial. ^bN = no. ^cY = yes.

SCID: severe combined immunodeficiency

Table 3. Causes of neonatal lymphopenia (abnormal T-cell receptor excision circle levels at birth) [8,9]

Cause	Comment
SCID and leaky SCID	–
T-cell impairment syndromes	<i>DiGeorge syndrome, Down syndrome, ATM mutation</i>
Secondary T-cell impairment	<i>Cardiac malformation, chylous effusion, maternal medication (azathioprine)</i>
Prematurity	–
“Idiopathic” lymphopenia	<i>Transient or moderate</i>

SCID: severe combined immunodeficiency.

Table 4. Significance of differences in recall rates between pairs of gestational-age subgroups after Bonferroni correction for multiple comparisons. Recall rates for (A) appointments, (B) second dried blood spot samples, and (C) either appointments or second dried blood spot samples are considered.

A	<28	[28–33]	[33–37]
[28–33]	0.013		
[33–37]	<0.001	0.30	
≥37	<0.001	<0.001	0.06

B	<28	[28–33]	[33–37]
[28–33]	<0.001		
[33–37]	<0.001	<0.001	
≥37	<0.001	<0.001	<0.001

C	<28	[28–33]	[33–37]
[28–33]	<0.001		
[33–37]	<0.001	<0.001	
≥37	<0.001	<0.001	<0.001