Newborn screening for severe immunodeficiency: Advantage in the case of early treatment

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The German Institute for Quality and Efficiency in Health Care (IQWiG) assessed the benefit of newborn screening for severe combined immunodeficiency (SCID). Without treatment most young children with SCID die within 1 to 2 years, as their immune response fails.

The benefit assessment provides a hint of a benefit of newborn screening for SCID: An early test combined with infection prophylaxis and subsequent curative treatment (allogeneic bone marrow or stem cell transplantation) can prevent severe or deadly infections in affected children.

Severe and extremely rare disease in young children

The failure of immune response in SCID is caused by a genetic disorder leading to inhibited development of vital immune cells (T lymphocytes, B lymphocytes, natural killer cells). Children with SCID are already highly susceptible to infections as babies and also show impairment of growth.

Without treatment most young children with SCID die within 1 to 2 years. It is not exactly known how many children are born with SCID in Germany. For the year 2013, statistics of the statutory health insurance report 21 cases in children younger than a year old.

Standard treatment: infection prophylaxis and transplantation

SCID is currently treated with allogeneic bone marrow or stem cell transplantation: In this procedure, the inadequate stem cells of the child are replaced by those of a suitable donor in order to develop the child's immune function. The question of the optimum time of transplantation and the necessity of chemotherapy in newborns with SCID is currently the subject of controversy.

Even before initiation of curative treatment the newborns must be stabilized by preventive and supportive measures, such as strict hygienic precautionary measures, infection prophylaxis, and substitution of antibodies.

Routine screening currently without SCID

In Germany an extended newborn screening programme is conducted for the early detection of diseases that could endanger physical or mental development. In its Paediatric Directive, the Federal Joint Committee (G-BA) specifies which diseases this programme covers and which tests are to be used.

Screening for SCID is currently not included there. In newborn screening, among other things dried blood taken 48 to 72 hours after birth is analysed, which could also be used to determine the child's immune status and thus to diagnose SCID.

The G-BA commissioned IQWiG to assess the benefit and harm of newborn screening for SCID in combination with curative treatment. The goal is to identify children with SCID even before occurrence of the first infection and ideally to start curative treatment at an early stage.

This aims to increase the likelihood of preventing harms and deaths.

Data still sketchy: study results still lacking

Because SCID is an extremely rare and severe disease, IQWiG allowed a broad methodological framework for the benefit assessment: from analyses of single components of the screening chain to studies of a low evidence level, such as retrospective analyses. Two controlled intervention studies provided evaluable results on mortality.

Data on the occurrence of infections (morbidity) were reported only incompletely; this is why no conclusion on benefit is possible for this outcome. No study results were available for any other outcomes (e.g. hospital stays, developmental impairment, and health-related quality of life). An intervention study in France is running until June 2018 and data on benefit can also be expected.

The earlier the treatment, the fewer the number of deaths

A retrospective data analysis of 108 children in 2 English hospitals showed a marked difference between treatment groups. There were 6 deaths (10%) in the group of 60 patients with an early start of treatment, while there were 29 deaths (60%) in the control group of 48 patients with a later start of treatment.

A second study showed a clear advantage for earlier (age 3.5 months): 1 of 21 children (5%) died in the intervention group, whereas 25 of 96 children (26%) died in the control group.

Overall, a hint of a benefit of an earlier start of treatment with infection prophylaxis and subsequent stem cell transplantation can be derived

from the data. The certainty of results is restricted by the study design (non-randomized and retrospective) and the incompleteness of data.

Diagnostic accuracy: screening test identifies SCID, but error rate unclear

The data from 5 relevant diagnostic accuracy studies are insufficient to calculate sensitivity and specificity; for this reason the number of false-negative and true-negative results is unclear. However, this test is basically suitable for identifying newborns with SCID.

It is unclear how many children with SCID are not identified. In the ongoing French study, data on sensitivity and specificity are also to be collected up to 2018, so that this sub-question can also soon be answered more precisely.

Overall, on the basis of the data available on the frequency (prevalence) of disease, in the German healthcare context it can be assumed that screening all roughly 700,000 newborns per year for SCID can identify all roughly 20 to 30 affected newborns. In the screening test the concentration of T cells in filter card blood is measured (T-cell receptor excision circle [TREC] analysis).

Potential harm is limited

As positive test results can be clarified by a subsequent gene test, unnecessary treatments through screening are not to be expected. However, parents could suffer from potential harm caused by a false-positive test result - they are under psychological stress while waiting for the result of the gene test, even if it ultimately indicates an "all-clear".

Harmful consequences of false-negative test results are conceivable if

other signs of SCID are not followed up with further diagnostics due to the inconspicuous test result. It would then be possible that necessary medical interventions are delayed; however, in the present case this seems very unlikely. Moreover, a negative test result does not exclude newborns from the other examinations conducted according to the current diagnostic standard.

Process of report production

IQWiG published the preliminary results in the form of the preliminary report in July 2016 and interested parties were invited to submit comments. At the end of the commenting procedure, the preliminary report was revised and sent as a final report to the commissioning agency in November 2016. The written comments submitted were published in a separate document together with the final report. The report was produced in collaboration with external experts.

An English-language extract of the final report will be available soon. If you would like to be informed when this document is available, please send an e-mail to info@iqwig.de.

More information: www.iqwig.de/en/projects-resul … -screening.6805.html

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