Spinal muscular atrophy (SMA): Newborn screening promises a benefit

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On behalf of the Federal Joint Committee (G-BA), the Institute for Quality and Efficiency in Health Care (IQWiG) investigated whether it is meaningful to test newborns in Germany for spinal muscular atrophy (SMA) in combination with earlier diagnosis and treatment. The Institute's final report is now available.

After evaluating the evidence available, the IQWiG researchers see an

indication of a benefit of newborn screening versus no screening: The earlier the disease is diagnosed and the earlier doctors can thus start treatment, the greater the benefit for children with an early onset of disease (infantile SMA). The advantages are mainly seen in better motor development, such as the achievement of motor milestones like "free sitting" and "walking".

Genetically related muscle atrophy is rare, but extremely serious

5q-associated SMA is a hereditary disease that leads to the progressive death of motor nerve cells (motor neurons) in the spinal cord and thus to muscle atrophy and weakness.

With about one new case per 10,000 infants, infantile SMA is very rare, but extremely serious: the muscle weakness impairs or even prevents motor development (e.g. "free sitting" and "walking") as well as lung function. If left untreated, the increasing symptoms of infantile SMA ultimately lead to the need for permanent ventilation and to death. In the equally rare forms with a later onset of disease, the course is usually milder and less predictable.

Blood sample is sufficient—effective treatment is available

The aim of newborn screening for 5q-associated SMA is the earlier identification and thus the earliest possible (ideally pre-symptomatic) start of treatment of the children affected. However, SMA is not yet one of the diseases that are examined in extended newborn screening. In this screening programme conducted in Germany in accordance with the G-BA's paediatric directive, venous or heel blood is collected in the 36th to 72nd hour of life, dripped onto filter paper cards and examined for the

presence of certain diseases.

For drug therapy of SMA, a drug called nusinersen (approved since 2017) is available in Germany. Nusinersen replaces the effect of defective genes and is administered via a puncture of the spinal cord canal (lumbar puncture). Other new therapeutic approaches are currently undergoing review for approval.

Linked evidence approach used

IQWiG project manager Andrea Steinzen explains: "No direct evidence was available for this benefit assessment, i.e., there were no comparative intervention studies of the screening chain. We therefore had to compile the evidence ourselves, using various pieces of the puzzle from treatment and diagnostic studies and following the so-called "linked evidence" approach. For the final report, at our insistence the manufacturer provided a crucial piece of the puzzle to assess the effects of starting treatment earlier, which ultimately led to an indication of a benefit of newborn screening".

In order to compare an early start of treatment in symptomatic children suffering from SMA (i.e. within at most 12 weeks after symptom onset) with a later start, the IQWiG researchers evaluated a small randomized controlled trial (RCT) investigating drug therapy versus sham treatment. With regard to the combined outcome "time to death or permanent ventilation" and the outcome "achievement of motor milestones" (e.g. "free sitting" and "walking"), the children affected benefited from an early start of treatment.

In the commenting procedure, the manufacturer subsequently submitted the results of a second study comparing a start of treatment in pre-symptomatic children with an early start of treatment in symptomatic children. The study results showed a dramatic effect in favour of the

former with regard to the outcome "achievement of motor milestones". Andrea Steinzen: "The earlier treatment can start, the more positively the course of the disease is influenced".

Due to the short observation period in both studies of less than or exactly one year, no conclusions can be drawn on long-term results. With regard to adverse effects, no differences were shown in either study between the different starting times of treatment. For other outcomes, there are no usable data on these comparisons.

To evaluate the diagnostic accuracy of the test procedures, the IQWiG project team was able to use four studies, the results of which indicate that the test procedures investigated are suitable for screening newborns for 5q-associated SMA.

Important ethical implications still unclear

Newborn screening also identifies newborns with a probable late onset of disease (i.e. symptoms that do not appear until years later). However, the available data on children with infantile SMA do not allow conclusions as to whether children with a late onset of disease who were identified by screening would also benefit from a pre-symptomatic start of treatment. This is because treatment data on children with infantile SMA cannot be automatically transferred to other forms of SMA. The introduction of newborn screening for SMA should therefore include consideration of appropriate management of these children and their families, including the potential option of choosing to be informed (or not) about the presence of mild forms of SMA.

Process of report production

IQWiG published the preliminary results, the preliminary report, in

October 2019 for discussion. After the commenting procedure, the project team revised the preliminary report and sent it to the contracting agency, the G-BA, as a final report in February 2020. The written comments submitted are published in a separate document at the same time as the final report.

More information: Final Report: www.iqwig.de/en/projects-resul … rophy-sma.10782.html

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