Health Council of the Netherlands

Neonatal screening for OCTN2 deficiency

executive summary

Primary carnitine deficiency (also known as organic cation transporter 2 (OCTN2) deficiency) is a rare hereditary metabolic disease. Approximately 1 in 100.000 children are born with the disease. There is wide variability in the severity of the disease. The benign form often does not lead to health problems. The severe form of the disease can lead to life-threatening low blood sugar levels, liver disease or heart problems, often during the first year of life. Without treatment, children with the severe form of OCTN2 deficiency can die. Timely treatment completely prevents these problems. A large proportion of people with OCTN2 deficiency have the benign form and for these people, there is no benefit from treatment.

Since 2007, OCTN2 deficiency has been detected as an incidental finding in the newborn blood spot screening programme in the Netherlands. The newborn blood spot screening programme screens newborns for 27 severe, but treatable, diseases. OCTN2 deficiency is not one of the target diseases, but nevertheless, it can be detected as part of the screening.

In 2005, the Health Council of the Netherlands advised adding OCTN2 deficiency as a target disease to the newborn blood spot screening programme. However, a feasibility study conducted by the National Institute for Public Health and the Environment (RIVM) found that more research was needed into the benefits and feasibility of this. In 2023, results of a comprehensive study on OCTN2 deficiency in the Netherlands (the ODIN study) were published. The State Secretary of Health, Welfare and Sport asked the Health Council to provide advice based on the new research findings, on whether adding OCTN2 deficiency as a target disease to the newborn blood spot screening programme would be meet the criteria for responsible screening. This advice has been prepared by the Committee on Preconception, Prenatal and Neonatal Screening.

Screening with OCTN2 deficiency as an incidental finding not desirable

In the current newborn screening programme, OCTN2 deficiency is not formally a target disease: it is not one of the diseases which are screened for. The disease is detected because of the screening method used. The screening lab uses a particular quality parameter, the total amount of free carnitine in the blood. A low free carnitine level can indicate that the test results are unreliable, and the child is therefore referred for further diagnostic tests. A low free carnitine level can also indicate OCTN2 deficiency. By using the free carnitine level as a screening parameter,

children are in practice screened for OCTN2 deficiency, even though it is not a target disease in the screening programme. In addition, recent research has shown that no target diseases are missed if the free carnitine level is low. Therefore, measuring this parameter is no longer required to ensure the quality of the programme.

The continuation of the current screening practice, in which OCTN2 deficiency is considered to be an incidental finding, is not desirable. According to the committee, incidental findings should be avoided where possible. If there is sufficient reason to screen for OCTN2 deficiency, then the disease must meet the criteria for population screening. Monitoring and evaluation to ensure the quality of screening only take place for target diseases; at the moment, this is not the case for OCTN2 deficiency.

According to the committee, there are only two possible outcomes of this advice: either OCTN2 deficiency will be added as a target disease to the newborn blood spot screening programme, or it will be removed completely so that is no longer detected as an incidental finding. If it is added as a target disease, there will be no changes to the programme for children with OCTN2 deficiency and their parents compared to the current situation because, with the current policy, these children are identified and can be treated so that severe symptoms or death are avoided. If OCTN2 deficiency was no longer detected, then children with severe OCTN2 deficiency would run the risk of severe, irreversible health problems.

In this advice, the committee reviews in which of these scenarios the balance between the benefits and harms of screening is most favourable.

Health benefits gained through screening outweigh the harms

If OCTN2 deficiency is added to the screening programme as a target disease, then, according to the committee, only the severe form of the disease should be screened for. The benign forms of the disease rarely cause health problems and therefore, people with these forms do not need to be treated. The committee used the criteria from the Health Council report *Neonatal Screening: new recommendations* to decide if the severe form of OCTN2 deficiency should be added as a target disease.

If OCTN2 deficiency was made a target disease, severe illness or death of one child would be prevented every 3 to 4 years. Without screening, these children would develop severe health problems and may die. Through screening, these children can be treated before the onset of symptoms. The relatively inexpensive treatment (lifelong intake of carnitine supplements) is extremely effective: it completely prevents the development of symptoms. According to the committee, these health benefits are significant. Although there are a small number of children who would benefit from screening, the health benefit gained per child is very high.

On the other hand, the current method for screening results in a high number of false positive screening tests. Because of this, there are children who undergo diagnostic tests and short-term treatment with carnitine supplementation although this is, in retrospect, unnecessary.
The committee finds this relatively high number of false positives acceptable because of the high health benefits and the possibilities for optimalisation of the screening test if OCTN2 deficiency is added as a target disease.

Diagnostic pathway reduces the harms of screening

In the Netherlands, all children are treated by whom health benefits can be gained. This is due to the use of DNA-testing to differentiate between the benign and severe forms of OCTN2 deficiency. In addition, the diagnostic pathway can be followed quickly so that children and their parents are burdened as little as possible.

Mothers in the Netherlands are also no longer tested for OCTN2 deficiency if their child does not have the condition. A test result indicating OCTN2 deficiency in a child can, in some cases, be caused by OCTN2 deficiency in the mother. The benefits of referring these mothers for additional testing do not outweigh the harms. In the last 14 years, the majority of the mothers who were tested had the benign form of OCTN2 deficiency. Only one mother had the severe form, although she had never experienced any symptoms. In other countries, mothers are tested and treated, which is seen as a significant harm of screening.

The committee also considered the cost-effectiveness of adding OCTN2 deficiency as a target disease to the screening programme. The estimated extra costs (including diagnostic costs) are considered by the committee to be proportional: every few years, screening prevents serious illness or death of a child. This is in line with what is acceptable for the screening programme as a whole.

Advice: add OCTN2 deficiency as a target disease

The committee advises to add OCTN2 deficiency as a target disease in the newborn blood spot screening programme. The health benefits for newborns with the disease are so large that this outweighs the harms for children without the disease who are referred for diagnostic testing. The committee, however, emphasises the importance of improving the balance of benefits and harms of screening. The committee expects that the test characteristics can be improved through optimalisation, should OCTN2 deficiency be added as a target disease. The committee also expects that the screening can be further improved through new developments in promising screening techniques. With these techniques, it will be possible over the longer term to differentiate between the benign and severe forms of the disease with the screening test itself.

The committee advises that screening for OCTN2 deficiency be evaluated in ten years' time.

Finally, the committee points out that expansion of the newborn blood spot screening programme is complex and cost-intensive, despite the health benefits gained. Aside from OCTN2 deficiency, there are more (sometimes less rare) conditions that could possibly be eligible for newborn screening. This could potentially lead to difficult choices in the future. The capacity that is required for a high-quality screening programme will need to be considered in the future when making decisions about the newborn blood spot screening programme.

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