Neonatal screening for spinal muscular atrophy

No. 2019/15, The Hague, July 23, 2019

Executive summary

Health Council of the Netherlands

This advisory report addresses the question of whether spinal muscular atrophy (SMA) should be included in the neonatal blood spot screening. SMA mostly affects young children; it causes paralysis and can be fatal. A new treatment for SMA has been available on the European market since 2017. It appears that this is more effective if it is commenced earlier in the progression of the condition. The Committee on preconception, prenatal and neonatal screening has tested SMA against the criteria for neonatal screening.

SMA is serious

SMA is a serious condition that is diagnosed in approximately fifteen young children in the Netherlands annually. It is caused by two mutations in the *SMN1* gene. The result is that much less SMN protein is produced, causing a loss of motor neurons (nerve cells that control motion) followed by increasing loss of muscle. Once the damage has occurred, it is irreversible. Because *SMN1* is not functioning, patients depend on *SMN2* for the production of SMN protein. This gene produces much less functional SMN protein. The more copies of *SMN2* an SMA patient has, the less severe the illness will be. Therefore, there are variants of SMA (types 1 to 4) that vary in severity. The more severe variants become manifest at a young age. Patients with SMA type 1 never learn to sit up and do not live beyond the age of two years. The illness only becomes manifest in patients with the type 4 variant in adulthood and they have a normal life expectancy. 60% of children with SMA have type 1, 25 to 30% have type 2 and 10 to 15% have type 3.

There is a good treatment available

A drug called nusinersen reduces the symptoms of SMA in at least half of the patients treated. The earlier treatment is commenced, the greater the effect. Because nusinersen has only recently come onto the market, research into presymptomatic treatment (before the symptoms have occurred) has not yet been completed. The provisional results are however highly promising. In the future, gene therapy may be an even better treatment. This has however not yet been licensed for use on the European market.

The tests are of good quality

Various tests are available that can demonstrate the presence of SMA. The quality of these tests is good. Further investigations are needed to see how they perform in practice in the Netherlands, how many patients with an uncertain prognosis are detected, and how many incidental findings there are.

Screening would-be parents for SMA carrier status

An addition to neonatal screening could be screening people who want to have children to see if they are SMA carriers. This would allow them to make choices such as opting for preimplantation genetic diagnosis, prenatal diagnosis during pregnancy, or using donor reproductive cells.

Recommendation: include SMA in the neonatal blood spot screening with an evaluation

The committee recommends that SMA be included in the neonatal blood spot screening. The main benefit is that screening makes it possible to treat children before they develop symptoms. This represents a health benefit compared to the current situation. Children with SMA are currently diagnosed and treated once they have developed symptoms and irreversible damage has already occurred to the nervous system.

There are also disadvantages to SMA screening. The most significant disadvantage is that a group of children will be detected in whom it is not clear whether treatment is needed because, although they have no functional *SMN1*, they do have relatively many copies of *SMN2*. A proportion of these children will remain free of symptoms until an advanced age, or possibly permanently. There are also possible incidental findings, such as carrier status. The committee believes that the health gains that can be obtained by screening outweigh these disadvantages.

The committee recommends further validation of the test and the development of a protocol for referral, counseling and treatment, prior to implementation of screening. The committee emphasises the importance of evaluation of screening after five and ten years, since data is scarce on the quality of the tests, the effects of presymptomatic treatment and the longer term results of the treatment. As SMA remains a serious condition even with treatment, the committee recommends considering an offer of preconception screening in order to give parents (to be) reproductive options.

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Preferred citation:
Health Council of the Netherlands. Neonatal screening for spinal muscular atrophy.
The Hague: Health Council of the Netherlands, 2019; publication no. 2019/15.