Newborn infant screening for spinal muscular atrophy: Chances and challenges

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With the development of causally oriented therapies for 5q-associated spinal muscular atrophy (SMA), the disease course has changed dramatically. However, the results of available studies clearly indicate that the timing at which therapy is initiated is critical to therapeutic success. It is also apparent that high-grade motor neuron loss cannot be reversed by any of these therapies. Since the disease in most cases starts in early infancy, it is obvious to include 5q-associated SMA in general newborn infant screening (NBS). In recent years, pilot programs like those in Germany, Belgium, and the USA, as well as SMA screening, have been included in routine care in numerous countries. In other countries, however, the discussion process about ethical and financial aspect of NBS has not yet been completed.

The data available from screening projects clearly show that NBS and thus early treatment dramatically improves the prognosis compared to the natural disease course.[1] Although there is no doubt about the usefulness of NBS, problems in its implementation must be proactively addressed. These problems range from possible negative influences on the acceptance of previously established screening programs; logistical problems in the timely shipment of samples; difficulties in laboratory analysis; limitation of available therapy due to economic reasons; to the complex needs of identified children and their families.

The paper by D'Silva et al.[2] describes in detail the experience and difficulties in a large pilot project that began in 2018. It was found that overall readiness for NBS was not adversely affected. Similar experiences have been found in other pilot studies. A survey in Japan showed that the acceptance of NBS for SMA in the general population was 95%.[3] This was due to the respondents' belief that early therapy is definitely more effective than late therapy, regardless of the respondents' specific knowledge of the disease.

The methodology used in the study by D'Silva et al. was able to identify all affected children correctly. The fact that laboratory analysis for confirmation was inadvertently omitted in one child highlights the need for a tracking system to ensure that such errors are avoided whenever possible. Because the laboratory diagnostics in the study were performed in only one laboratory, it cannot be ruled out that additional technical errors may occur when similar programs are rolled out in larger countries with several different laboratories involved.

What is unusual is the extremely low number of children with four copies of *SMN2* in the Australian population compared with data found in other countries. The question arises whether this can be explained by a peculiarity of the Australian population compared with other populations or whether it can be explained by methodological problems in the precise determination of copy number.[4] This problem has been addressed in several studies. Incorrect copy number determination may lead to therapeutic errors in countries where therapeutic decisions are based on *SMN2* copy number. Thus, early therapy may not be initiated in cases where four instead of three *SMN2* copies were erroneously detected.[5]

The Australian study clearly demonstrates the need to standardize procedures and to involve the various stakeholders (such as healthcare providers and payers) in the screening process in a structured way, to thus create a functioning network in order to enable timely therapy. In about a quarter of the patients, first symptoms were already visible within the first 4 weeks of life; in other studies, signs of SMA were already found at the first presentation after screening.[1] This emphasizes the reality that successful NBS for SMA is a race against time.

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