Experts encourage earlier intervention for some infants with spinal muscular atrophy

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Spinal muscular atrophy (SMA), the most common form of neurodegenerative disease in childhood, is caused by defects in the SMN1 gene. SMA patients potentially benefit from three recently

approved disease-modifying therapies. These treatments are most effective if they are administered early or even before the onset of symptoms, but they are expensive. Guidelines have suggested a "watchful waiting" strategy for infants who are born with SMA and have more than two copies of the SMN2 gene. Multiple copies of SMN2 may compensate for the defect of SMN1 and make it possible that first symptoms of SMA occur later in childhood or even adulthood.

In a new study published in the *Journal of Neuromuscular Diseases*, investigators found that, on the contrary, a surprisingly large proportion of some infants with four copies of the SMN2 gene, whose families decided to postpone treatment, showed the first signs of disease between the ages of 1.5 and 4 years.

"The discussion in the SMA treatment community about the appropriate timing of therapy always includes the possibility that SMA might not manifest until adulthood, and many years of treatment could be avoided," explained lead investigator Dr. Katharina Vill, Department of Pediatric Neurology and Developmental Medicine and LMU Center for Children with Medical Complexity, Dr. von Hauner Children's Hospital, LMU Hospital, Ludwig-Maximilians-University, Munich, Germany. "However, there is a lack of detailed knowledge about the type and timing of initial symptoms. With the availability of new medications there is an urgent need to gain more knowledge about the 'how and when' of SMA onset."

While SMA is caused by a biallelic defect in the SMN1 gene itself, a closely related gene, SMN2, can ameliorate this deficiency. The vast majority of individuals with two or three copies of SMN2 begin to show symptoms in the first months of life. Patients with four or more copies of SMN2 develop symptoms later, possibly not before adulthood, and generally have milder symptoms. Guidelines published in 2018 recommended a "watchful waiting" approach for treatment in children

with SMA and four or more SMN2 copies. The guidelines were revised in 2020 to recommend pre-symptomatic treatment for these children, although no suggestion was made regarding when to start therapy.

The study conducted by Dr. Vill and colleagues enrolled 18 children born between January 2018 and January 2021. Long-term follow up was available for 15 children. All learned to sit independently and walk with assistance at age-appropriate times as expected for healthy children. Swallowing and feeding were normal in all patients. When the treatment guidelines changed in 2020, pre-symptomatic treatment was recommended to all patient families in the study.

"The change in treatment strategy midway through the pilot led to different parental decisions regarding how to proceed, particularly for children born in the first two years of the pilot. These families had initially been told that a wait and see strategy was acceptable, and several wanted to stick with it," Dr. Vill observed.

The families of eight of the 15 patients decided to start pre-symptomatic therapy with Nusinersen or Risdiplam in their children, who ranged in age from 3 months to 36 months. None of these children have shown any symptoms of disease to date (age 12-33 months). Seven of the families had not decided on treatment, and their children were closely monitored. Five of these seven children showed disease onset between 1.5 and 4 years of age.

One of these untreated patients developed proximal weakness at the age of 20 months, despite completely normal clinical findings at the age of 19 months. Treatment with Risdiplam for this child was initiated, but symptoms did not resolve. Three untreated children showed mild motor symptoms, two at 2 years and one at 3 years, with decreased endurance and tendency to fall. Therapy with Nusinersen in two of them and Risdiplam in one was initiated. The fifth child was found to have

neurogenic changes at 1.5 years, but no motor symptoms, and treatment with Risdiplam was initiated.

Early initiation of treatment in this cohort of patients is more expensive for the general healthcare system, but the investigators note that SMA causes high economic impact in terms of health and social costs, and that the quality of life for the affected children is extremely impaired.

"While the sample size is small, a very high number of children (five out of seven) became symptomatic in the first four years of life, with at least one showing irreversible symptoms. The proportion was much higher than expected," Dr. Vill said.

"Children with four copies of SMN2 have the most favorable genetic conditions for a good outcome under therapy. The 'wait and see' strategy might entail the risk of irreversible deficits for these patients. We recommend encouraging parents to start a treatment regimen early in childhood. If the parents decide to wait, follow up should be performed with extreme care."

While timing of treatment initiation remains unclear, the investigators note that they did not observe any symptoms in children before the age of 1.5 years.

More information: Astrid Blaschek et al, Newborn Screening for SMA—Can a Wait-and-See Strategy be Responsibly Justified in Patients With Four SMN2 Copies?, *Journal of Neuromuscular Diseases* (2022). DOI: 10.3233/JND-221510

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