Gene therapy delivered early can help children with rare neurodegenerative disease retain motor and cognitive functions

by Fondazione Telethon

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If administered early, gene therapy has the potential to change the medical history of children born with metachromatic leukodystrophy (MLD), a rare and lethal neurodegenerative disease of genetic origin which leads to the progressive loss of the ability to walk, talk and interact.

This was confirmed by a study published in the *New England Journal of Medicine* which showed that the therapy, if administered early, is able to preserve motor function and cognitive abilities in most patients.

The study was conducted on 39 children with MLD at the San Raffaele Hospital in Milan, Italy by clinical researchers Francesca Fumagalli and Valeria Calbi, under the coordination of Alessandro Aiuti, deputy director of the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget), head of the Pediatric Immunohematology Operating Unit at the IRCCS San Raffaele Hospital in Milan and full professor of Pediatrics at the Vita-Salute San Raffaele University.

This therapy was approved in the EU in 2020 and has been available and reimbursed in Italy since 2022: it is the result of more than 20 years of research conducted at SR-Tiget and of the strategic alliance between Fondazione Telethon and Ospedale San Raffaele with the anglo-american company Orchard Therapeutics, which holds the license both in the EU and in the US.

The results of the study

In the course of the study, patients with MLD were treated with gene therapy based on genetically corrected hematopoietic stem cells and the results were then compared with those of 49 untreated patients. Among the key indicators to assess the effectiveness of the therapy, the researchers considered the impact on motor skills (ability to walk or sit unsupported), cognitive skills (ability to speak or perform specific tests) and survival more generally.

The study confirmed that even in the long term, gene therapy can significantly reduce the risk of severe motor and cognitive impairment in all subgroups of patients treated: those with the late-infantile form, in which the onset of symptoms is expected between 6 months and 2½ years, those with the early-juvenile form, in which the onset is expected between 2½ and 6 years, treated in the pre-symptomatic phase of the disease, and early-juvenile patients treated in the presence of mild symptoms, albeit with less efficacy than for motor symptoms.

As the study's first authors, Francesca Fumagalli and Valeria Calbi, explain, "Most of the children treated before the onset of symptoms retained their ability to walk, whereas this was lost in the first years of life in all the children in the control group, who had not received gene therapy because they were already symptomatic or because they had been diagnosed when the therapy was not yet available.

"In many cases, these were the older brothers or sisters of the children who then received the treatment and who made it possible to diagnose the disease in their younger siblings: we would like to emphasize the generosity of the families of these patients, because without them we would not have been able to know the natural progression of the disease over time so well and to better evaluate the effects of the therapy.

"As far as cognitive development is concerned, we have observed a significant benefit in almost all treated patients, who continue to acquire new cognitive skills compared to the control group with severe cognitive impairment and loss of all ability to communicate."

In the light of these data collected over 12 years, which confirm that the positive effects of gene therapy are maintained over time, it becomes a priority to diagnose the disease early so as to maximize the effectiveness of treatment.

"Thanks to research, we have a therapy available that can change the course of a serious and unfortunately fatal disease without intervention, but is only effective if acted upon in time. This is why it is essential to have a newborn screening test for MLD as soon as possible, in order to diagnose the disease when it has not yet manifested itself," said Aiuti.

"A delay in diagnosis can, in fact, irretrievably preclude the possibility of intervening with gene therapy. Often the diagnosis comes too late, or 'thanks' to an older brother or sister who has already been diagnosed and cannot be treated."

What is metachromatic leukodystrophy?

Metachromatic leukodystrophy (MLD) is caused by mutations in a gene responsible for the metabolism of particular substances called sulfatides, which, if not disposed of properly accumulate particularly in the central and peripheral nervous system.

In the most severe forms, these children rapidly lose the ability to walk, talk and interact with the world around them: most of them die in infancy and have only palliative care available to them. It is estimated that 1 in every 100,000 children globally is born with this disease every year.

Gene therapy

It is administered via a single infusion after chemotherapy to make room for the correct cells and is approved in the EU and the US. It is indicated for children with the late-infantile or juvenile-early-onset forms who have not yet manifested clinical signs of the disease, and for those with the juvenile-

early-onset form who, although presenting the first clinical manifestations, are still able to walk independently and have not yet shown a decline in cognitive abilities..

Newborn screening for MLD

Newborn screening is a simple, non-invasive test and is one of the main public preventive medicine programs. By means of a test carried out on a blood sample taken from the heel of each newborn baby during the first three days of life, it makes it possible to identify at an early stage a number of genetic metabolic diseases on which dietary or pharmacological treatment can be applied.

In Italy, thanks to Law 167, since 2016 this test has been extended nationwide to more than 40 diseases: according to the Italian Society for the Study of Metabolic Hereditary Diseases and Neonatal Screening (SIMMESN), approximately 350 Italian children could receive a life-saving diagnosis each year.

MLD is currently not among the diseases subject to newborn screening, neither in Italy nor in the rest of the world (only Norway is an exception). However, more than a dozen pilot studies are underway, two of which are in Italy: one started in March 2023 in Tuscany, coordinated by the AOU Meyer IRCCS in Florence and financed also thanks to the Voa Voa Amici di Sofia Association, and one started in July 2024 in Lombardy, promoted by Fondazione Telethon thanks to an agreement with the Buzzi Children's Hospital Foundation and coordinated by the Vittore Buzzi Children's Hospital in Milan. .

To date, in the context of these pilot studies, it has been possible to diagnose MLD early in four children, three in Germany and one in the United Kingdom, who were offered the opportunity of gene therapy at an early stage. As far as the Italian studies are concerned, to date none of the approximately 50,000 babies screened in Tuscany and Lombardy has tested positive.

More information: Francesca Fumagalli et al, Long-Term Effects of Atidarsagene Autotemcel for Metachromatic Leukodystrophy, *New England Journal of Medicine* (2025). DOI: 10.1056/NEJMoa2405727

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