Baby born deaf can hear after breakthrough gene therapy

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Baby Opal and mother Jo. Credit: Cambridge University Hospitals NHS Foundation Trust

A baby girl born deaf can hear unaided for the first time, after receiving gene therapy when she was 11 months old at Addenbrooke's Hospital in Cambridge.

Opal Sandy from Oxfordshire is the first patient treated in a global gene therapy trial, which shows "mind-blowing" results. She is the first British patient in the world and the youngest child to receive this type of

treatment.

Opal was born completely deaf because of a rare genetic condition, auditory neuropathy, caused by the disruption of nerve impulses traveling from the inner ear to the brain.

Within four weeks of having the gene therapy infusion to her right ear, Opal responded to sound, even with the cochlear implant in her left ear switched off.

Clinicians noticed continuous improvement in Opal's hearing in the weeks afterwards. At 24 weeks, they confirmed Opal had close to normal hearing levels for soft sounds, such as whispering, in her treated ear.

Now 18 months old, Opal can respond to her parents' voices and can communicate words such as "Dada" and "bye-bye."

Opal's mother, Jo Sandy, said, "When Opal could first hear us clapping unaided it was mind-blowing—we were so happy when the clinical team confirmed at 24 weeks that her hearing was also picking up softer sounds and speech. The phrase 'near normal' hearing was used and everyone was so excited such amazing results had been achieved."

Auditory neuropathy can be due to a variation in a single gene, known as the OTOF gene. The gene produces a protein called otoferlin, needed to allow the inner hair cells in the ear to communicate with the hearing nerve. Approximately 20,000 people across the U.K., Germany, France, Spain, and Italy and are deaf due to a mutation in the OTOF gene.

The CHORD trial, which started in May 2023, aims to show whether gene therapy can provide hearing for children born with auditory neuropathy.

Professor Manohar Bance from the Department of Clinical Neurosciences at the University of Cambridge and an ear surgeon at Cambridge University Hospitals NHS Foundation Trust is chief investigator of the trial. He said, "These results are spectacular and better than I expected.

"Gene therapy has been the future of otology and audiology for many years and I'm so excited that it is now finally here. This is hopefully the start of a new era for gene therapies for the inner ear and many types of hearing loss."

Children with a variation in the OTOF gene often pass the newborn screening, as the hair cells are working, but they are not talking to the nerve. It means this hearing loss is not commonly detected until children are 2 or 3 years of age—when a delay in speech is likely to be noticed.

Professor Bance added, "We have a short time frame to intervene because of the rapid pace of brain development at this age. Delays in the diagnosis can also cause confusion for families as the many reasons for delayed speech and late intervention can impact a children's development.

"More than 60 years after the cochlear implant was first invented—the standard of care treatment for patients with OTOF related hearing loss—this trial shows gene therapy could provide a future alternative.

"It marks a new era in the treatment for deafness. It also supports the development of other gene therapies that may prove to make a difference in other genetic related hearing conditions, many of which are more common than auditory neuropathy."

Mutations in the OTOF gene can be identified by standard NHS genetic testing. Opal was identified as being at risk as her older sister has the

condition; this was confirmed by genetic test result when she was 3 weeks old.

Opal was given an infusion containing a harmless virus (AAV1). It delivers a working copy of the OTOF gene and is delivered via an injection in the cochlea during surgery under general anesthesia. During surgery, while Opal was given the gene therapy in right ear, a cochlear implant was fitted in her left ear.

James Sandy, Opal's father said, "It was our ultimate goal for Opal to hear all the speech sounds. It's already making a difference to our day-to-day lives, like at bath-time or swimming, when Opal can't wear her cochlear implant. We feel so proud to have contributed to such pivotal findings, which will hopefully help other children like Opal and their families in the future."

Opal's 24-week results, alongside other scientific data from the CHORD trial are being presented at the American Society of Gene and Cell Therapy (ASGC) in Baltimore, U.S. this week.

Dr. Richard Brown, Consultant Pediatrician at CUH, who is an Investigator on the CHORD trial, said, "The development of genomic medicine and alternative treatments is vital for patients worldwide, and increasingly offers hope to children with previously incurable disorders. It is likely that in the long run such treatments require less follow up so may prove to be an attractive option, including within the developing world. Follow up appointments have shown effective results so far with no adverse reactions and it is exciting to see the results to date.

"Within the new planned Cambridge Children's Hospital, we look forward to having a genomic center of excellence which will support patients from across the region to access the testing they need, and the best treatment, at the right time."

Patients are being enrolled in the CHORD trial in the U.S., U.K. and Spain.

Patients in the first phase of the study receive a low dose to one ear. The second phase are expected to use a higher dose of gene therapy in one ear only, following proven safety of the starting dose. The third phase will look at gene therapy in both ears with the dose selected after ensuring the safety and effectiveness in parts 1 and 2. Follow up appointments will continue for five years for enrolled patients, which will show how patients adapt to understand speech in the longer term.

Provided by University of Cambridge