EuroSciCon

JOINT EVENT
28th International Conference on
Neuroscience and Neurochemistry
&
28th Euro-Global Neurologists Meeting

June 13-14, 2019
Barcelona, Spain

Mitra Assadi et al., J Neurol Neurosci 2019, Volume 10

Gene and cell-based treatments for Canavan disease

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Canavan disease (CD) is a severe childhood leukodystrophy caused by homozygous mutations in the aspartoacylase (ASPA) gene. Several mutations have been detected in Jewish and non-Jewish families. We share our experience on the natural history of CD as well as treatment responses in a total of 34 cases with genetically confirmed CD.

In the absence of ASPA activity, large amounts of N-acetyl-aspartate (NAA) accumulate in the brain. This creates an osmotic pressure resulting in spongiform degeneration, macrocephaly and biosynthesis defect in myelination. The afflicted children suffer severe developmental regression despite the best conservative management and die prior to reaching their 10th birthday. We observed the natural history of CD in a cohort of 28 patients, out of which 13 received gene therapy. Using quantitative T1 sequences on the brain MRI, we monitored the brain volume and the myelin content. As expected, the untreated children demonstrated progressive brain atrophy and loss of myelin.

Proton MRS (HMRS) was utilized to quantify the NAA levels in target regions in the cortex and basal ganglia. While in normal children the whole brain NAA level peaks at about 6 months of age, our data indicated that in children affected with CD, and NAA levels continue to increase with an anterior–posterior gradient ($p<0.0001$).

We enrolled 13 patients in the gene therapy trial using AAV vector which was delivered through direct parenchymal injection into the frontal, parietal and occipital regions of the brain. The intervention resulted in a decrease in elevated NAA levels and slowed progression of the brain atrophy. A significant drop in the NAA level was noted in the frontal ($p<0.0008$), peri-ventricular ($p<0.00012$) and basal ganglia ($p<0.00049$). Clinically speaking, using the Gross Motor Function Measure (GMFM), we demonstrated a small but statistically significant improvement in the motor milestones ($p<0.017$). Moreover, an improvement in the seizure frequency and overall stabilization of the clinical status was noted. 5-year follow-up indicated that the gene therapy was safe and the administration of the AAV vector was not associated with any long-term adverse effects.

Six cases were enrolled in a separate trial using lithium citrate 45 mg/kg/day for a period of 2 month and the above primary endpoints were utilized to assess the efficacy of the treatment. The HMRS demonstrated a modest drop in the NAA levels in the above regions of interest, reaching statistical significance in the basal ganglia ($p<0.02$). The GMFM scores did not demonstrate any significant improvement in the motor milestones.

In conclusion, both the gene therapy and use of lithium citrate are safe in CD and effective in reducing the NAA levels in the brain.

Biography

Mitra Assadi is director of the Headache Medicine and Pediatric Neurology at the Capital Institute for Neurosciences. Board certified in neurology and clinical neurophysiology; she was among one of the first neurologists in the United States to obtain a board certification in headache medicine in 2008. She is actively involved in teaching and research. She is a Professor of Neurology at Robert Wood Johnson Medical School and the Director of the Neurology Clerkship at Capital Health system. Her research has mostly focused on neuro-genetic disorders, in particular leukodystrophies. She has served as a clinical investigator at the Center for Cell and Gene Therapy at the Rowan University since 2004. She has special expertise in Canavan Disease and her published research on the use of lithium in Canavan patients has established the standard of care for these patients in the scientific community.

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