VIEWPOINT

Newborn Screening and Emerging Therapies for X-Linked Adrenoleukodystrophy

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Newborn screening and gene therapy are exciting new advances in the field of metabolic neurodegenerative disorders. This Viewpoint discusses X-linked adrenoleukodystrophy (ALD), an inherited disorder affecting the adrenals and nervous system white matter. X-linked adrenoleukodystrophy is caused by mutations in the gene *ABCD1*, which maps to Xq28 and encodes the adrenoleukodystrophy protein. This protein is an ATP-binding cassette transporter that facilitates the transport of very-long-chain fatty acids (VLCFA) into the peroxisome for degradation. *ABCD1* mutations lead to an increase in VLCFA in all tissues. There are at least 2552 known *ABCD1* mutations, of which 759 are nonrecurrent, and there is no genotype-phenotype correlation, even within the same family.[1]

The birth incidence of ALD in North America was predicted to be 1 in 17 000, a statistic that has been found to be 1 in 14 700 live births by 2.7 years of newborn screening in the state of New York.[2,3] The 2 most common neurologic phenotypes in males with ALD are the childhood cerebral ALD (CCALD) form, a rapidly progressive neuroinflammatory disease with typical age at onset at 2 to 10 years (35%) and the adult spinal cord disease, adrenomyeloneuropathy (AMN), with age at onset of 20 to 30 years (60%).[1] Left untreated, 90% of CCALD cases result in death or vegetative state within 2 years after symptom onset, while AMN progresses slowly over decades.[4] A semiquantitative 34-point scale based on extent of magnetic resonance imaging (MRI) lesion in different brain regions has been developed by Daniel Loes, referred to as the Loes score, to determine disease severity in CCALD, with 0 being normal.[5] Boys with a score of less than 3 are neurologically asymptomatic,[4] while most boys with neurological symptoms have a score of 10 or higher. Independent of the neurological presentation, about 90% of males with ALD also develop adrenal insufficiency at some point during life.[1] Approximately 65% of women heterozygous for ALD also present with neurological symptoms of AMN by age 60 years, with a range of symptoms from mild to severe disability.[1] The female neurological phenotype resembles more closely the adult AMN variant, and cerebral inflammatory demyelination as seen in males with ALD is exceptionally rare. Also, adrenal insufficiency is rare in females with ALD.[1]

Historically, the diagnosis of CCALD in boys was established by the characteristic pattern of cerebral demyelination found in ALD[4] by neuroimaging and confirmed by biochemical measurement of plasma total lipid VLCFA,[6] following early symptoms of attention-deficit/hyperactivity disorder, failure in school, cognitive and behavior disturbances, or decline in handwriting. However, the currently available therapies of allogeneic hematopoietic stem cell transplantat (HSCT), either with bone marrow or cord blood cell, are ineffective in most boys with CCALD when treated with a Loes score greater than 9.[7,8]

While adrenal insufficiency should be closely monitored and is easily treatable with hormonal supplementation, the neurological aspects of ALD are far more challenging to treat. The most established therapy for CCALD is allogeneic HSCT. This procedure has been shown to arrest disease progression only if done at the first sign of abnormal brain MRI prior to the onset of any neurological symptoms.[7,8] However, HSCT is associated with high morbidity and some mortality. The outcomes are further improved by using a matched related rather than unrelated bone marrow or cord blood donor.[8] Yet graft rejection, graft-vs-host disease, and associated long-term immunosuppression remain a major challenge and cause of morbidity. At present, no disease-modifying therapy exists for the AMN phenotype.

Following the death of their son, Aidan, owing to complications of a late HSCT for ALD, the Seeger family drafted Aidan's Law and lobbied the New York State legislators for ALD newborn screening, and on December 30, 2013, ALD newborn screening began in New York. After several years of successful lobbying by scientists and ALD families, the former US Secretary of Human Health and Human Services signed the recommendation to add ALD to the uniform panel of disorders screened in the newborn period in all states in the United States in 2016. California, Connecticut, Minnesota, and Pennsylvania have commenced screening for ALD, and other states have legislation in place to add ALD to the newborn screening panel. It is our hope that ALD newborn screening will expand to all US states within the next 5 years, thus improving the clinical outcome of hundreds of infants with ALD and their relatives.

With the rising rate of newly diagnosed newborns with ALD, there is an urgent need for novel therapies. While several therapeutic targets are being considered, such as increasing the expression of ALD-related protein, *ABCD2*, the most promising results so far are emerging from an ex vivo gene therapy trial: the goal of the STARBEAM study was to stop CCALD cerebral disease progression by using autologous HSCT with ex vivo gene transfer using a Lentiviral vector to avoid complications associated with allogeneic transplant.[9] The candidates for this ex vivo gene therapy study had an MRI score of 0.5 to 9 and did not have a human leukocyte antigen–matched sibling donor for HSCT. The interim results of this study show stabilization of MRI severity score and lack of major functional disability, with minimal clinical symptoms in 15 of 17 boys in the study. One of the boys in the STARBEAM study had rapid neurologic de-

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terioration and died of disease progression following his transplant, and a second boy, who had evidence of disease progression on MRI, withdrew from the study to undergo allogeneic HSCT and later died of transplant-related complications.[9] These results resemble previously reported disease stabilization seen in CCALD with allogeneic HSCT. Further monitoring of these individuals is needed to assess long-term effectiveness and safety of this new therapeutic modality.

The hope is that ex vivo gene therapy will become the standard of care for boys with ALD identified by newborn screening once MRI lesions develop. All families with male and female infants with ALD should receive genetic counseling. Male infants with ALD should be followed up by a pediatric endocrinologist starting during the first few months of life because hormone therapy for adrenal insufficiency is well established.[10] In addition, boys should be referred to a pediatric neurologist and receive annual MRI between 1 to 2 years of age and then every 6 months from ages 3 to 12 years and yearly thereafter to detect early CCALD that would be treated with either HSCT if there is a human leukocyte antigen–matched sibling donor or ex vivo gene transplant if there is no matched donor. Boys and girls with ALD are normal at birth; thus, there is a window of opportunity for these therapies following early diagnosis through newborn screening. There is hope that ongoing preclinical research and other emerging trials will also lead to therapies for the adult AMN phenotype.

ARTICLE INFORMATION

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