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Childhood Cerebral Adrenoleukodystrophy: A Review of Current Knowledge

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ALD is an X-linked peroxisomal disorder with a 1 in 20,000 - 30,000 live births incidence estimate [1]. It is caused by mutations in the adenosine triphosphate (ATP)-binding cassette subfamily D member 1 (ABCD1) (ALDP) gene, which encodes the peroxisomal membrane ALD protein [2]. The transport of very-long-chain fatty acids (VLCFAs) into peroxisomes is impeded in the absence of ALDP, resulting in their breakdown.

VLCFAs build in the plasma, brain, and spinal cord as a result, and adrenal glands of patients with ALD [3].

Childhood cerebral adrenoleukodystrophy (CALD), adolescent cerebral form, adult cerebral form, adrenomyeloneuropathy (AMN), olivo-ponto-cerebellar form, and Addison's disease are all clinical phenotypes. The most common phenotype is CALD, which is distinguished by the progression of intellectual, psychological, visual and gait abnormalities at school age. CALD that is not treated tends to progress predictably [4].

Boys usually exhibit behavioral or academic decline initially, which may be misinterpreted as attention deficit/hyperactivity disorder. Typically, the illness progresses to impairments in visual/auditory function, gait abnormalities, incontinence episodes, bulbar dysfunction, and seizures. Major functional disabilities (MFDs) such as loss of communication, cortical blindness, tube feeding reliance, total incontinence, wheelchair dependence, complete loss of voluntary movement, and death from neurologic deterioration develop gradually in affected males. The Neurologic Function Score can be used to grade CALD clinical symptoms (NFS) [5].

During childhood, male children with ALD are at a high risk of developing neurological problems. devastating cerebral ALD (highest incidence 4 - 8 years of age) and primary adrenal insufficiency (peak incidence 3 - 10 years of age), both of which, if discovered before to onset of symptoms, have life-saving medications available [6].

Primary adrenal insufficiency is a commonly missed diagnosis [7]. The clinical signs and symptoms of hyperpigmentation, poor growth (initially in weight), hypotension, hypoglycemia, weakness, and unexplained nausea/decreased appetite progressively develop and are commonly attributed to other more prevalent conditions [8].

With the development of a biochemical assay, extended family screening could be performed, expanding the population of asymptomatic males. Monitoring for adrenal insufficiency and magnetic resonance imaging (MRI) for cerebral disease could be performed in the at-risk population. ACTH levels were found to be abnormal in males at very early ages prior to overt adrenal disease [9].

Early identification and treatment of CALD is a challenge [10]. Most important, the addition of adrenoleukodystrophy to the Recommended Uniform Screening Program has provided a new opportunity to alter the natural history of the disease by monitoring for CALD from birth [11].

The screening of newborns for ALD is now standard practice in the United States of America (24 states) and the District of Columbia, however there are still challenges, some expected and some unforeseen [12]. The fundamental issue remains the variation in screening from state to state.

Before the onset of neurologic symptoms, symmetric contiguous white matter lesions can be seen on standard MRI in early disease. Gadolinium enhancement (GdE+), a marker of active inflammation in the brain, is regarded as a significant prognostic biomarker of rapidly progressive disease when present [13]. The Loes score (range, 0 to 34) is used to quantify the areas of white matter involvement in CALD MRI disease severity [14].

Treatments currently based on allogeneic hematopoietic stem cell transplantation (HSCT) and the use of a

low VLCFAs diet (Lorenzo's oil) and on bone marrow transplantations [15].

The 47th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT 2021) (March 14-17, 2021) featured a Presidential Symposium, new data from the clinical development program for elivaldo-, Updated data from the pivotal Phase 2/3 Starbeam study (ALD-102) and the long-term follow- up study LTF-304 on gene autotemcel (eli-cel, Lenti-DTM) gene therapy in patients with CALD have been presented.as well as the ALD-104 Phase 3 study's safety findings.

Eli-cel is a one-time investigational gene therapy designed to add functional copies of the ABCD1 gene into a patient's own hematopoietic (blood) stem cells (HSCs) that have been transduced *ex vivo* with the Lenti-D lentiviral vector. Patients can now produce the adrenoleukodystrophy protein (ALDP), which activates the breakdown of VLCFAs, thanks to the addition of the functioning ABCD1 gene. The purpose of eli-cel treatment is to slow the progression of CALD and hence maintain as much neurological function as feasible. Importantly, eli-cel does not require the use of donor HSCs from another person [16].

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