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The Landscape of Hematopoietic Stem Cell Transplant and Gene Therapy for X-Linked Adrenoleukodystrophy

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Abstract

Purpose of review To present an updated appraisal of hematopoietic stem cell transplant (HSCT) and gene therapy for X-linked adrenoleukodystrophy (ALD) in the setting of a novel, presymptomatic approach to disease.
Recent findings Outcomes in HSCT for ALD have been optimized over time due to early patient detection, improved myeloablative conditioning regimens, and adjunctive treatment for patients with advanced cerebral disease. Gene therapy has arrested disease progression in a cohort of boys with childhood cerebral ALD. New therapeutic strategies have provided the clinical basis for the implementation of Newborn Screening (NBS). With the help of advocacy groups, NBS has been implemented, allowing for MRI screening for the onset of cerebral ALD from birth.
Summary Gene therapy and optimized hematopoietic stem cell transplant for childhood CALD have changed the natural history of this previously devastating neurological disease.

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Introduction

X-linked adrenoleukodystrophy (ALD) is caused by mutations in the *ABCD1* gene [1]. *ABCD1* encodes the peroxisome transporter protein ATP-binding cassette domain 1 (ABCD1). ABCD1 dysfunction leads to the accumulation of very long chain fatty acids (VLCFAs) in plasma and tissues, specifically the testes, adrenal glands, and central nervous system [2]. Multiple phenotypes emerge with no established genotype-phenotype relationship [3]. Thirty-five to 40% of boys, and to a lesser degree adult men, will undergo inflammatory cerebral ALD (CALD), which is characterized by microglial apoptosis, blood brain barrier dysfunction, and inflammatory demyelination [1, 4, 5]. Conversely, a smaller subset of patients with cerebral ALD will spontaneously arrest, and are not eligible for transplant [3, 6, 7]. Brain lesions in CALD appear on MRI prior to the onset of clinical symptoms [8•]. At the time of symptom, onset inflammatory CALD is rapidly progressive and results in a vegetative state or death in 2–3 years [1, 9]. Alternatively, 65% of patients will develop adrenomyeloneuropathy (AMN) in adulthood, resulting in slowly progressive gait disturbance, neuropathy, and bowel and bladder incontinence [10]. The estimated prevalence of ALD is about 1/17,000, however the recent institution of newborn screening suggests significantly higher rates of disease [11, 12].

The following report will review the biological insights which led to stem cell–based gene correction, data-driven improvements in clinical outcomes for hematopoietic stem cell transplant (HSCT) [9], a new option for the treatment of childhood CALD [13••], and a gene-based therapeutic approach for patients with AMN [14••]. Importantly, the approach to ALD is in transition; newborn screening (NBS) has provided the opportunity to monitor patients from birth [11]. This provides new insights into the natural history of disease, specifically an understanding of early lesion development, which informs the implementation and timing of intervention [8•].

Biological rationale for gene correction: Hematopoietic stem cell transplant to gene therapy

The benefit of replacing a patient's bone marrow cell population, and thereby the deficient enzyme, with a donor had been clinically demonstrated by treating patients with lysosomal and peroxisomal storage disorders since the early 1990s [15]. The monocyte-macrophage-microglial cell line was proposed as the effector cell in correcting the CNS phenotype [16]. The initial evidence came from non-CNS organ correction (Kupffer cells in liver, pulmonary macrophages in lung). Bone marrow–derived monocytes enter the CNS via the lepto-meninges, choroid plexus, and across the blood brain barrier (perivascular space) and differentiate into microglia [15, 17]. In ALD specifically, bone marrow–derived cells expressing functional ABCD1 protein confer the ability to metabolize VLCFAs to non-functional cells through cell-to-cell contact [18].

Hugo Moser proposed gene therapy for ALD in 1994 [19]. He put forth the following appraisal of ALD against the proposed criteria required for the success of a gene-based therapeutic approach:

(1) The gene causing the disease, *ABCD1*, is known

(2) The natural history and pathogenesis has been well studied

(3) The disease causes serious disability that cannot be treated by current methods, but could be diagnosed prior to symptom onset

(4) The affected gene's activity does not require delicate control; it is usually present in excess, so that replacement of a fraction of normal ABCD1 protein activity can be of benefit

(5) *ABCD1* gene activity can be measured indirectly by a surrogate marker—the level of VLCFA

(6) HSCT is effective in halting CALD.

At the time, researchers had the most experience with retroviruses [19]. When tested in vitro, a recombinant retrovirus successfully transfected skin fibroblasts from childhood CALD and AMN patients with the *ABCD1* gene, and subsequently normalized VLCFA levels [20]. Doerflinger et al. transfected a stem cell population (CD34+) using a similar method and found the cells not only normalized VLCFA levels, but proliferated as well [21]. This set the stage for transfecting non-ABCD1 expressing CD34+ cells from ALD patients. Once transduced to express functional ABCD1, the cells were grafted into 18 mice. Although only three mice engrafted successfully, the cells developed into ABCD1-expressing monocytes [17]. This set of experiments provided the pre-clinical proof of concept that would frame the first gene therapy clinical trial in childhood cerebral ALD.

Hematopoietic stem cell transplantation for adrenoleukodystrophy

Hematopoietic stem cell transplantation is the standard of care for patients diagnosed with cerebral adrenoleukodystrophy. It is able to halt the progression of disease. Traditionally, overall morbidity and mortality was high [1, 22].

Improvements in transplant outcomes have resulted from studying and refining the transplant procedure, and by identifying patients earlier in the disease course. Here, we will review the major updates in HSCT for CALD.

HSCT in early cerebral ALD leads to improved survival and function

In 2000, Shapiro et al. reported the long-term beneficial effect of HSCT in CALD [23]. More importantly, they reported the specific benefit of preserved neurological function if transplanted early in the disease course, especially while patients are presymptomatic. Peters and later Mahmood et al. provided further clarification in their respective follow up studies in expanded cohorts [22, 24]. They reported 92–95% survival in patients who underwent HSCT with 0 or 1 neurological deficits, and an MRI score < 9 (range 0–34) [25]. Since then, the benefits of treating early CALD as defined above have been confirmed [9, 26] in the setting of overall improved survival over time [9, 27]. The clinical implications of improved outcomes from early CALD transplant were (1) a statement of need for newborn screening for ALD, and (2) it established the value of specific inclusion criteria for the first gene therapy trial for cerebral ALD.

Despite HSCT in early CALD, post-transplant neurocognitive outcomes vary and are predicted by the pre-transplant MRI score

In a retrospective review of 62 patients with early CALD who underwent HSCT, Pierpont et al. demonstrated a decline in long-term cognitive outcomes with higher pre-transplant MRI scores [28]. Patients with a pre-transplant MRI score < 4 retained neurocognitive function post-transplant, despite most having impairment in at least one domain. Only two patients performed within or above average range on all tasks at long-term follow-up, both of whom had a pre-transplant MRI score of 2. Otherwise, the remainder of patients (MRI score 4.5–9) declined in at least one domain post-HSCT. Again, this supported the recommendation for screening for cerebral ALD from birth with the aim of intervention at the earliest time point possible.

N-acetylcysteine improves outcomes in patients with advanced CALD

While progress was made in understanding the treatment of patients with early CALD, most patients with CALD currently have advanced disease. For patients with advanced CALD, HSCT is contraindicated not only due to morbidity and mortality of the procedure itself, but because late transplant has been shown to accelerate inflammatory demyelination and neurological decline [16].

Evidence of oxidative stress and damage are present in advanced CALD [29]. Powers et al. demonstrated evidence of reactive oxidative species and lipid peroxidation in the adrenal glands and brain of patients with cerebral ALD [30], which is not present in the mouse model for ALD. These findings were further confirmed when Rockenbach et al. demonstrated elevated lipid peroxidation in the blood of ALD patients, and subsequent reduction post-HSCT [31]. The proposed mechanism of oxidative stress was addressed by treating advanced CALD patients (MRI score > 14) with N-acetyl-L-cysteine in the peritransplant period [32]. This resulted in survival of the three treated patients, while all other patients died within the first year after transplant [33].

Optimization of the conditioning regimen in HSCT reduces toxicity and graft failure

While myeloablative chemotherapy is necessary replace the host bone marrow cells with donor cells, chemotherapeutic agents are well known to come with toxic side effects [34]. In ALD, neurotoxic side effects are particularly damaging as they can cause permanent regression in the peritransplant period. An initial strategy to minimize this risk was the replacement of cyclophosphamide with fludarabine given its effectiveness, with less toxicity, in combination myeloablation with busulfan [35]. Busulfan is necessary for full myeloablation, but it has been shown to cause veno-occlusive disease, hepatic toxicity, graft-versus-host disease (GVHD), and seizures in patients with ALD [27, 36]. Conversely, if overall exposure

to busulfan is too low, patients are at risk of graft failure. To address the need for a therapeutic total-exposure target range that limits graft failure and toxicity, Bartelink et al. performed a retrospective multicenter cohort analysis of 674 children who underwent a busulfan-based conditioning regimen for a stem cell transplant for both malignant and non-malignant indications [37]. By performing a cumulative area under the curve analysis (AUC), with event-free survival as the outcome of interest, the authors determined that a cumulative exposure between 78 mg h/L and 101 mg h/L, combined with fludarabine, predicted the highest event-free survival in children.

Hematopoietic stem cell transplant can arrest disease progression in adults with CALD

The second incidence peak for cerebral ALD occurs in adulthood where patients undergo the same form of inflammatory demyelination as in childhood [38]. Given the lack of treatment options, and rapid disease progression for inflammatory lesions, HSCT was trialed in 14 patients with adult CALD. Overall survival was 57%. Importantly, factors associated with overall and event-free survival were preserved functional status at the time of transplant defined as an Expanded Disability Status Scale (EDSS) < 6, stable cognition from diagnosis of cerebral ALD to HSCT, and an uncomplicated transplant course. The subgroup of patients with internal capsule involvement on MRI had higher mortality than those who did not [39]. Similar findings were reported 2 years later in a cohort of 15 men. Overall survival was 73%. Patients with no or mild cerebral or myelopathic symptoms had preserved neurological function.

Conversely, as noted prior, patients with internal capsule involvement on MRI had cognitive and motor deterioration on follow-up [40]. Taken together, these initial observations help guide recommendations for HSCT in the adult population.

Gene therapy for childhood cerebral adrenoleukodystrophy

Cartier et al. performed the first gene therapy in two patients with progressive inflammatory cerebral ALD. Wild-type *ABCD1* was transfected into the CD34+ cells of the two patients ex vivo via a self-inactivating lentiviral vector. The autologous transplant of corrected CD34+ cells led to functional ABCD1 protein detection in both patients in multiple cell lineages. Radiographically, cerebral disease halted. Clinically, both patients remained neurologically stable [41•].

These findings led to the STARBEAM trial where 17 boys with progressive inflammatory childhood CALD were treated with a hematopoietic stem cell transplant using autologous CD34+ stem cells corrected ex vivo with the lentiviral vector carrying wild-type *ABCD1*. Inclusion criteria reflected the patients with > 90% survival from the previous

20 years of HSCT experience: early CALD defined as 0 or 1 neurologic deficit and an MRI score < 9. Fifteen of 17 boys remained alive and free of major functional disabilities. Radiographically, brain lesions stabilized (Fig. 1). One patient died from rapid disease progression. One patient withdrew from the study due to evidence of disease progression, and died from HSCT complications [13••]. The results indicated that gene therapy for childhood CALD leads to clinical and radiographic

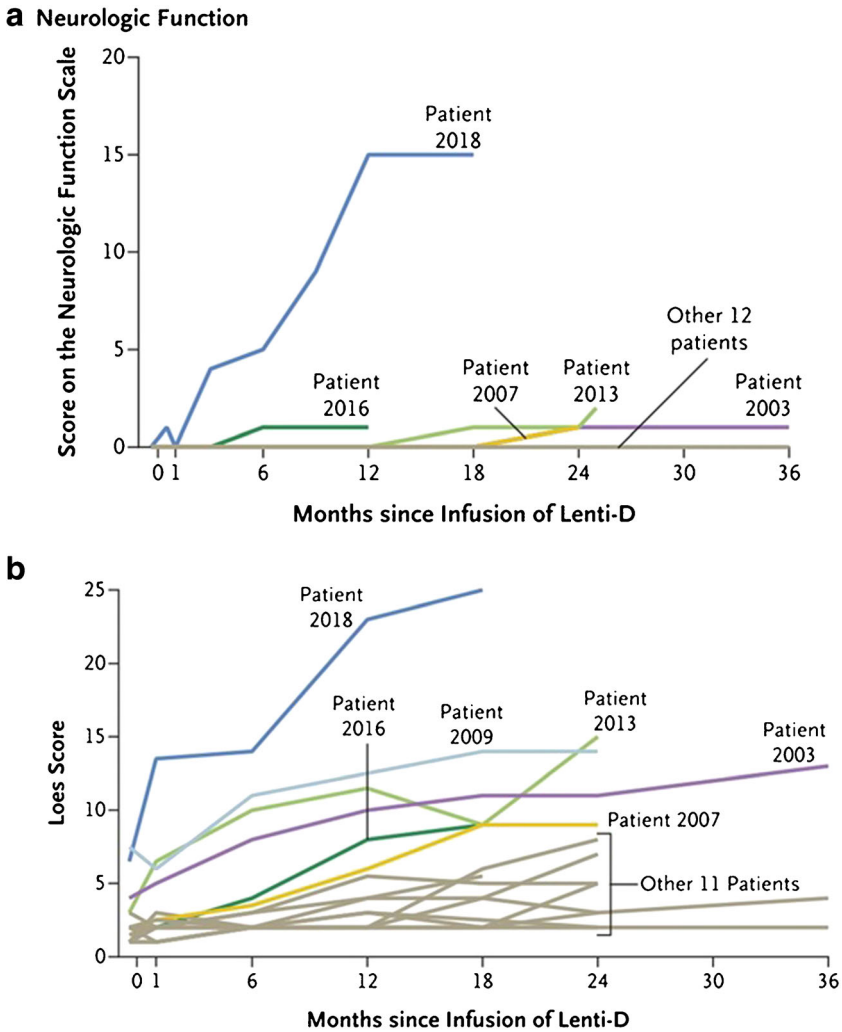

Fig. 1. Neurologic function and MRI outcomes after treatment with gene therapy. **a** Scores on the cerebral adrenoleukodystrophy–specific neurologic function scale (which ranges from 0 to 25, with higher scores indicating more severe deficits) for each of the 17 patients at various time points after the infusion of the Lenti-D drug product; 12 patients had scores of 0 at all time points, with the last measurement obtained at month 36 (in 3 patients), month 30 (2), month 24 (5), or month 18 (2). The scale is used to evaluate the severity of gross neurologic dysfunction through an assessment for 15 disabilities across multiple domains; a score of 0 indicates the absence of clinical signs of cerebral disease. **b** Shown are the Loes scores for each of the 17 patients at various time points after the infusion of the Lenti-D drug product. The Loes scores range from 0 to 34, with higher scores indicating an increased extent of lesions on magnetic resonance imaging (MRI). A score of 0.5 or less is considered to be normal. Adapted with permission from Eichler et al. 2017 [13••].

stabilization of disease. The expanded, international, follow-up gene therapy trial is currently ongoing.

Newborn screening and novel drug development, a multiple stakeholder approach

One of the most important interventions in ALD in the USA was its addition to the Recommended Uniform Screening Panel (RUSP). NBS was implemented through the extraordinary efforts of parents, patient advocacy groups, and healthcare professionals [11]. Prior to NBS, the delay in diagnosis of index cases of ALD was 9.9 years. The diagnosis only became apparent after irreversible neurologic deficits accrued [42], which translated to poor post-transplant quality of life for patients who survived [43]. With the implementation of newborn screening, patients

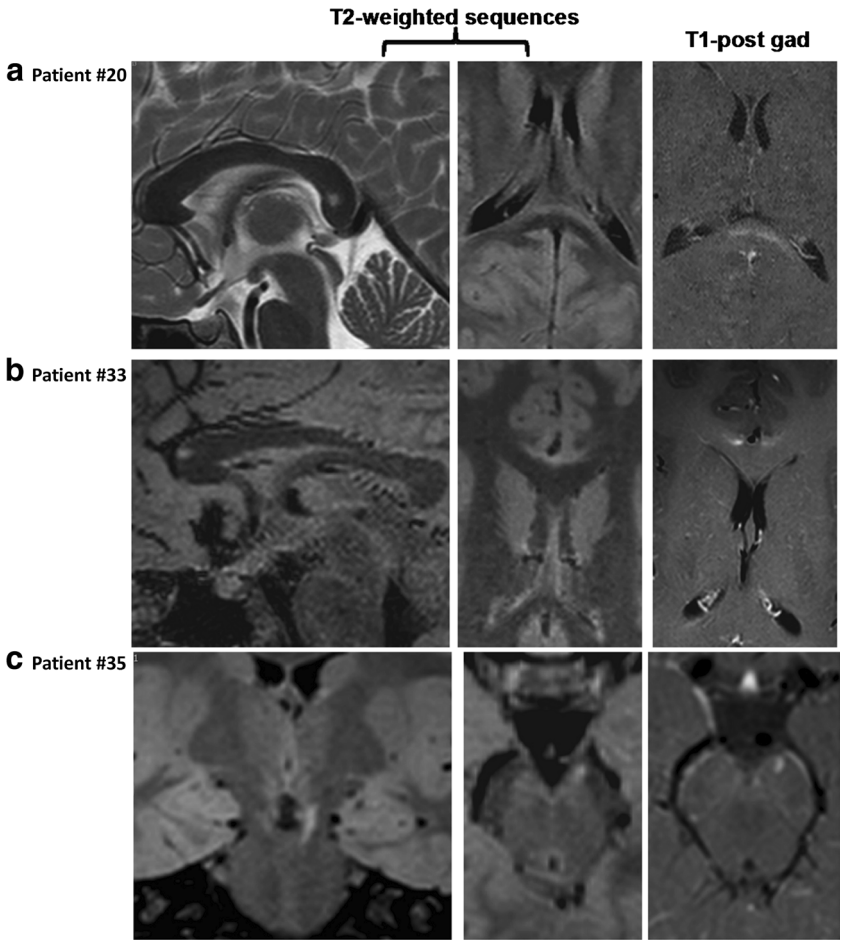

Fig. 2. Early lesions in childhood cerebral adrenoleukodystrophy. (A) An 8-year-old boy with a T2-hyperintense lesion in the splenium of the corpus callosum, Loes score of 1. (B) A 7.2-year-old boy with a lesion in the genu of the corpus callosum, Loes score of 1. (C) An 8.2-year-old boy with a lesion in the left frontopontine projection fibers, Loes score of 0.5. Contrast enhancement can be appreciated in all cases. Adapted with permission from Liberato et al. 2019 [8•].

can be monitored by MRI from birth for the early detection of cerebral lesions, with the aim of intervention in the "narrow window" prior to symptom onset (Fig. 2) [8•, 22, 44].

In ALD, the multiple stakeholder approach not only drove legislation for NBS, but the early development of the gene therapy for ALD. Families affected by the disease convened roundtables with neurologists, oncologists specializing in bone marrow transplantation, vectorologists, and physicians with experience in gene therapy to discuss a human gene therapy for ALD. They also contacted pharmaceutical companies developing viral vectors to explore the possibility of a gene therapy trial [45]. While the initial childhood CALD trial was ongoing, collaborations between parents, patient advocacy groups, and pharmaceutical companies supported trial recruitment, and the development of personalized therapy programs. Currently, those same relationships are helping gene therapy reach market [46].

On the horizon: gene therapy for adrenomyeloneuropathy

Despite the optimization of HSCT and the encouraging results from gene therapy for CALD, definitive treatments for AMN do not yet exist. Importantly, HSCT in for CALD in childhood does not prevent the development of AMN in adulthood [47]. This is consistent with the observation that the pathophysiology between inflammatory CALD and AMN, a non-inflammatory axonopathy, are distinct [48, 49].

To begin exploring gene-based treatment options for AMN, Gong et al. successfully transduced CNS cells in vitro with an adenoviral vector containing human *ABCD1* demonstrating localization of ABCD1-protein to the peroxisome, and subsequent decrease in VLCFAs [50]. A recent follow-up study aimed to maximize the mode of delivery, avoid off-target organ toxicity, and avoid the generation of systemic immunity by delivering the vector via an osmotic pump directly into the spinal cord in vivo. Again, the group demonstrated transduction of CNS cells, including astrocytes, neurons, and vascular endothelial cells, with reduction in VLCFAs [14••]. These findings lay the groundwork for transition to the clinic, and are particularly exciting in the era of previously successful intrathecal gene-based therapies [51, 52].

Conclusion

Optimization of HSCT, and the advent of gene therapy, for ALD have changed the natural history of childhood cerebral disease. As a result, a call for newborn screening arose. The addition of ALD to the RUSP was supported by improved neurological outcomes and the effective treatment adrenal insufficiency.

However, its successful implementation was due to the efforts of parents and patient advocates. NBS for ALD now allows for MRI monitoring for conversion to CALD from birth, thus providing the opportunity to treat boys in that "narrow window" prior to the onset of neurological symptoms.

Compliance with Ethical Standards

Conflict of Interest

Eric Mallack receives research support from the NINDS (5 K12 NS066274-08).
Bela Turk declares that he has no potential conflicts of interest.
Helena Yan declares that she has no potential conflicts of interest.
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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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