

Presymptomatic Lesion in Childhood Cerebral Adrenoleukodystrophy

Timing and Treatment

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Abstract

Background and Objectives

We sought to characterize the natural history and standard-of-care practices between the radiologic appearance of brain lesions, the appearance of lesional enhancement, and treatment with hematopoietic stem-cell transplant or gene therapy among boys diagnosed with presymptomatic childhood-onset cerebral adrenoleukodystrophy (CCALD).

Methods

We analyzed a multicenter, mixed retrospective/prospective cohort of patients diagnosed with presymptomatic CCALD (Neurologic Function Score = 0, Loes Score [LS] = 0.5–9.0, and age <13 years). Two time-to-event survival analyses were conducted: (1) time from CCALD lesion onset-to-lesional enhancement and (2) time from enhancement-to-treatment. The analysis was repeated in the subset of patients with (1) the earliest evidence of CCALD, defined as an MRI LS ≤ 1, and (2) patients diagnosed between 2016 and 2021.

Results

Seventy-one boys were diagnosed with presymptomatic cerebral lesions at a median age of 6.4 years [2.4–12.1] with a LS of 1.5 [0.5–9.0]. Fifty percent of patients had lesional enhancement at diagnosis. In the remaining 50%, the median Kaplan-Meier (KM)-estimate of time from diagnosis-to-lesional enhancement was 6.0 months (95% CI 3.6–17.8). The median KM-estimate of time from enhancement-to-treatment is 3.8 months (95% CI 2.8–5.9); 2 patients (4.2%) developed symptoms before treatment. Patients with a diagnostic LS ≤ 1 were younger (5.8 years [2.4–11.5]), had a time-to-enhancement of 4.7 months (95% CI 2.7–9.30), and were treated in 3.8 months (95% CI 3.1–7.1); no patients developed symptoms before treatment. Time from CCALD diagnosis-to-treatment decreased over the course of the study ($\rho = -0.401$, $p = 0.003$).

Discussion

Our findings offer a more refined understanding of the timing of lesion formation, enhancement, and treatment among boys with presymptomatic CCALD. These data offer benchmarks for standardizing clinical care and designing future clinical trials.

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Glossary

ALD = X-linked adrenoleukodystrophy; **CALD** = cerebral adrenoleukodystrophy; **CCALD** = childhood cerebral adrenoleukodystrophy; **HSCT** = hematopoietic stem-cell transplant; **IRB** = institutional review board; **KM** = Kaplan-Meier; **LO** = Lorenzo's Oil; **LS** = Loes Score; **NFS** = Neurologic Function Scale.

X-linked adrenoleukodystrophy (ALD) is a genetic disorder that results from mutations in the *ABCD1* gene. Pathogenic variants lead to the impairment of peroxisomal beta-oxidation resulting in the elevation of very long chain fatty acids which affect the nervous system and adrenal cortex.¹ Approximately one-third of men with ALD will develop a cerebral demyelinating lesion during childhood (CCALD). CCALD lesions typically originate in the corpus callosum as small T2 hyperintense lesions which enlarge concentrically over many months before eventually manifesting clinical symptoms.²⁻⁵ Contrast enhancement is often absent in early stages of lesion development, but its appearance is considered an ominous prognostic marker of lesion progression.⁶ Lesional contrast enhancement is the indication for treatment with hematopoietic stem-cell transplant (HSCT),^{6,7} including hematopoietic stem-cell gene therapy currently under investigation.⁸⁻¹⁰ HSCT effectively halts progression but entails substantial risks.^{11,12} Clinical outcomes are superior among patients who receive HSCT although lesions are still small, before the onset of neurologic symptoms.¹¹⁻¹⁷ Taken together, the clinical goal of treating actively progressing lesions that are still small and presymptomatic implies a narrow “window of opportunity” for optimal HSCT deployment. Newborn screening for ALD aims to maximize this presymptomatic window of opportunity¹⁸⁻²⁰ by monitoring prospectively for early CCALD lesions,²¹ but the boundaries of this treatment window remain poorly defined.^{12,13,17}

Our aim in this study was to clarify several key aspects of the CCALD treatment window. First, we set out to define the natural history of lesion-onset more precisely. Although past reports of CCALD onset have included patients manifesting symptomatic (i.e., large) and presymptomatic (i.e., small) lesions,²¹ we restricted our analysis to patients presenting only during the presymptomatic stage. Second, among presymptomatic lesions that were not yet enhancing, we sought to measure time-to-enhancement. Finally, we sought to measure time from lesion enhancement-to-HSCT infusion. These findings offer benchmarks for establishing clinical care standards and designing clinical trials for CCALD prevention and treatment.

Methods

Participants

We analyzed a mixed retrospective/prospective cohort of boys diagnosed with presymptomatic CCALD followed at Massachusetts General Hospital, Amsterdam University Medical Center, Weill Cornell Medicine, Stanford Health Care, and the Kennedy Krieger Institute between January 1, 1987, and July 1,

2021, by either extended family screening or newborn screening. Inclusion criteria for the study were (1) confirmed diagnosis of ALD defined by the presence of elevated very long chain fatty acids and/or a pathogenic mutation in *ABCD1*; (2) diagnosis of “early-stage disease”^{8,12} defined as the development of a characteristic demyelinating lesion on T2-weighted MRI^{5,7} with an MRI severity score, or Loes Score (LS, range 0–34),²² of 0.5–9.0; (3) childhood onset defined as age <13 years at cerebral adrenoleukodystrophy (CALD) diagnosis; and (4) neurologically presymptomatic at CALD diagnosis as defined by an Neurologic Function Scale (NFS, range 0–25) score of 0.³ Patients diagnosed with arrested CALD were excluded given the difference in natural history, and patients with self-halted disease do not qualify for HSCT or gene therapy.²³⁻²⁵ Excluded patients in this age range had radiographically stable lesions, with no change in LS for ≥6 months, no evidence of enhancement at any time point, no change in NFS, and remained untreated (although continuously monitored by MRI) at the time of this study. Participation in the Lorenzo's Oil trial did not preclude participation in this study.²⁶

Clinical and Imaging Data

Three primary end points were collected per participant from routine clinical care: date of CCALD diagnosis, date of first contrast-enhancing lesion, and date of treatment (Figure 1). Patient age, NFS, LS, and lesion pattern were collected at each date. Lesions were subdivided into 5 patterns according to their primary neuroanatomic distribution⁷: (1) parieto-occipital lobe white matter or splenium of the corpus callosum, (2) frontal lobe white matter or genu of the corpus callosum, (3) frontopontine or corticospinal projection fibers, (4) cerebellar white matter, and (5) global involvement. The presence (+) or absence (–) of lesional gadolinium contrast enhancement on T1 postcontrast MR imaging at each scan date was recorded. MRI scans were classified as enhancement negative if contrast was administered and no lesional enhancement was present or a noncontrast MRI was performed at that time point. Treatment was defined as the date the patient underwent HSCT or gene therapy.

Statistical Methods

Clinical and Imaging Characteristics

Continuous variables are reported as median and range. Categorical variables are reported as percentages. The unpaired Mann Whitney *U* test was used to compare the LS at diagnosis with the LS at first evidence of lesional enhancement, and LS between lesional enhancement and treatment. To quantify the potential relationships with age and LS at diagnosis and the emergence of cerebral inflammation, the

Figure 1 Visualization of Main Study Questions

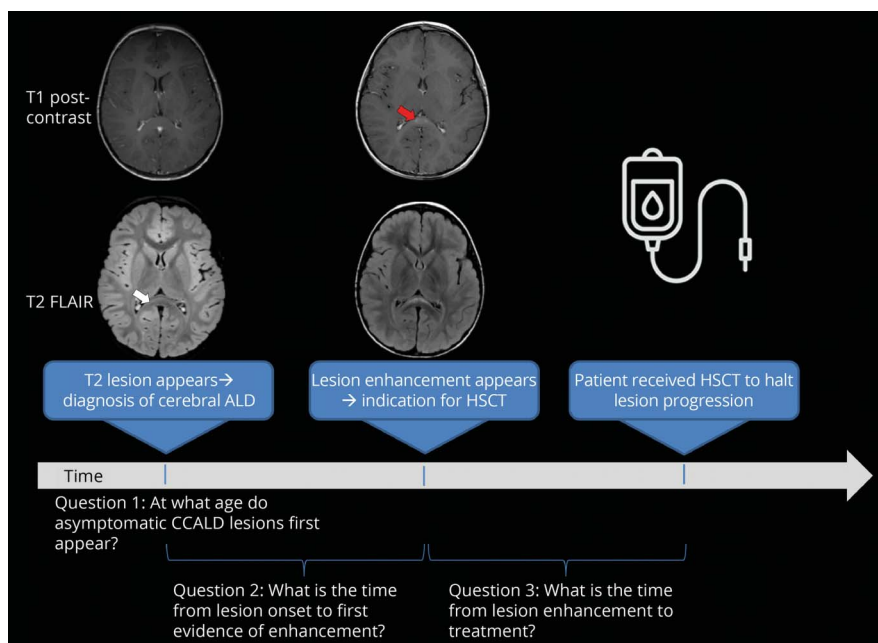


Illustration of the 3 primary analyses performed in this study: (1) age presymptomatic patients manifesting cerebral lesions, (2) measurement of time from diagnosis-to-enhancement, and (3) measurement of time from lesion enhancement-to-treatment.

Spearman rank correlation coefficient (ρ) was calculated between age of CCALD diagnosis and LS at diagnosis and time-to-lesional enhancement, respectively. Two-tailed tests with significance level of 0.5 were used to determine statistical significance. All data were annotated, analyzed, and visualized using RStudio (v.1.2.5033).

Primary Outcomes

Kaplan-Meier event-free survival was calculated from diagnosis of CCALD to the 2 major study end points: time from CCALD diagnosis-to-lesional enhancement and time from lesional enhancement-to-treatment (Figure 1). The results are plotted as cumulative incidence curves (1–Kaplan-Meier [KM] survival probability) and reported as median event-free survival and cumulative incidence ($[1\text{--KM survival probability}] \times 100\%$) of each outcome with 95% CIs.

Subgroup Analyses

To approximate the natural history of early lesions detected by newborn screening, the analysis was repeated in the subset of patients with a diagnostic LS ≤ 1.0 .

Finally, we hypothesized that treatment performance has improved over the duration of the study, likely because of improved MR scanner strength and resolution (i.e., 1.5T vs 3.0T), disease awareness, and newborn screening. To test this hypothesis, the Spearman rank correlation coefficient (ρ) was calculated between year of CCALD diagnosis and the time interval from diagnosis to treatment. A time-to-treatment analysis was performed on the subset of patients diagnosed with CCALD within the past 5 years (January 1, 2016, to July 1, 2021).

Standard Protocol Approvals, Registrations, and Patient Consents

Patients were identified through each institution's respective institutional review board (IRB)-approved clinical research protocol (IRB Protocols: WCM 19-08020583, Stanford IRB 59014, JHMI IRB00105090, AUMC METC 2014_347, MGH 2012P000132). Participant data were reviewed, deidentified, and storage was encrypted and password protected at each site. Deidentified data were then transferred to Weill Cornell Medicine through interinstitutional data use agreements. Owing to anonymization, consent was waived.

Data Availability

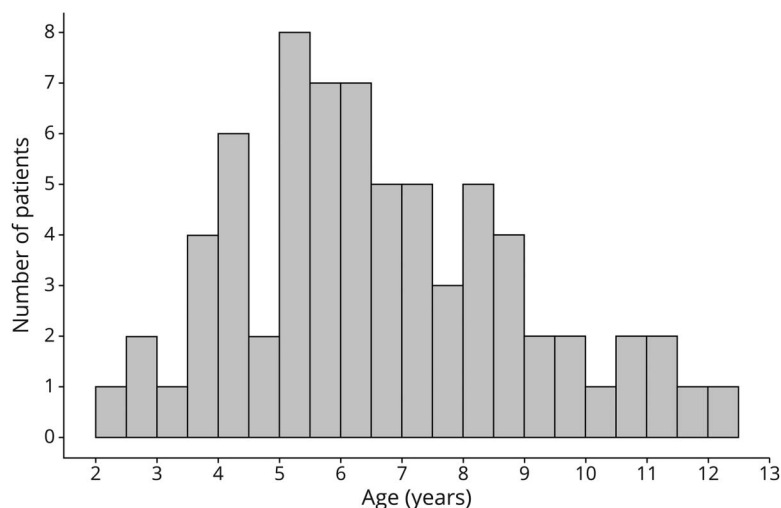
After publication, any data not published within this article will be anonymized and shared by request from any qualified investigator.

Results

Diagnosis of Presymptomatic Childhood Cerebral Adrenoleukodystrophy

We identified 71 patients who were presymptomatic at the time of their first abnormal MRI. The median age was 6.4 years (2.4–12.1) (Figure 2) with an initial LS of 1.5 (0.5–9.0). There is a weak relationship between LS and age at diagnosis ($\rho = 0.340$, $p = 0.004$). Splenial lesions were most common at diagnosis (pattern 1, 69.0%), followed by internal capsule and brainstem involvement (pattern 3, 14.1%), frontal lesions (pattern 2, 9.9%), combined splenial-internal capsular lesions (pattern 1, 3, 5.6%), and one patient with combined genu, splenium, and internal capsular involvement (pattern 1, 2, 3, 1.4%).

Figure 2 Age Distribution of Presymptomatic CCALD Diagnosis



Median age of 71 patients diagnosed with CCALD before symptom onset (NFS = 0) was 6.4 years (2.4–12.1) with an initial LS of 1.5 (0.5–9.0). CCALD = childhood cerebral adrenoleukodystrophy; LS = Loes Score; NFS = Neurologic Function Scale.

Time From Presymptomatic CCALD Diagnosis-to-Lesion Enhancement

There is no relationship between age of diagnosis and time from diagnosis-to-lesional enhancement ($\rho = 0.033$, $p = 0.822$). There is no significant difference in LS between CCALD diagnosis and lesional enhancement. Imaging data were available for 44 patients, all of whom (100%) were presymptomatic at detection of enhancement (Table). Imaging data were not available for 27 patients at this time point.

Two subgroups emerged in the analysis of time from CCALD diagnosis-to-lesional enhancement. Twenty-four patients had contrast-enhancing lesions at diagnosis (“immediate enhancement” subgroup). Twenty of 44 patients developed lesional enhancement after initial diagnosis, constituting the “delayed enhancement” subgroup. The median KM-estimate of time from diagnosis-to-lesional enhancement in the delayed enhancement cohort was 6.0 months (95% CI 3.6–17.8) (Figure 3). 81.5% (95% CI 53.0–92.7) of patients developed evidence of lesional inflammation by 18 months.

Notably, lesional enhancement “flickered on” in 3 patients; an early MRI revealed a gadolinium-enhancing lesion, followed by an MRI without lesional enhancement, which on continued

surveillance imaging again displayed positive enhancement 4.3–12.1 months from the initial enhancing scan.

Time From Lesional Enhancement-to-Treatment

The LS increased from detection of enhancement to treatment (median LS = 2.5 [0.5–11.0], $p = 0.044$). Forty-six of the 48 patients (95.8%) with available clinical data remained presymptomatic at treatment (Table). Two patients became symptomatic, each with an NFS = 2 at treatment: (1) a 3-year-old boy diagnosed with an initial LS = 4.0, mixed pattern 1 and 3 lesion distribution, with rapidly progressive disease who was transplanted 5 weeks after diagnosis and (2) a boy diagnosed at 7.2 years with a LS = 2.0 who was treated 26.1 months later after his parieto-occipital lesion expanded to a LS = 9.0.

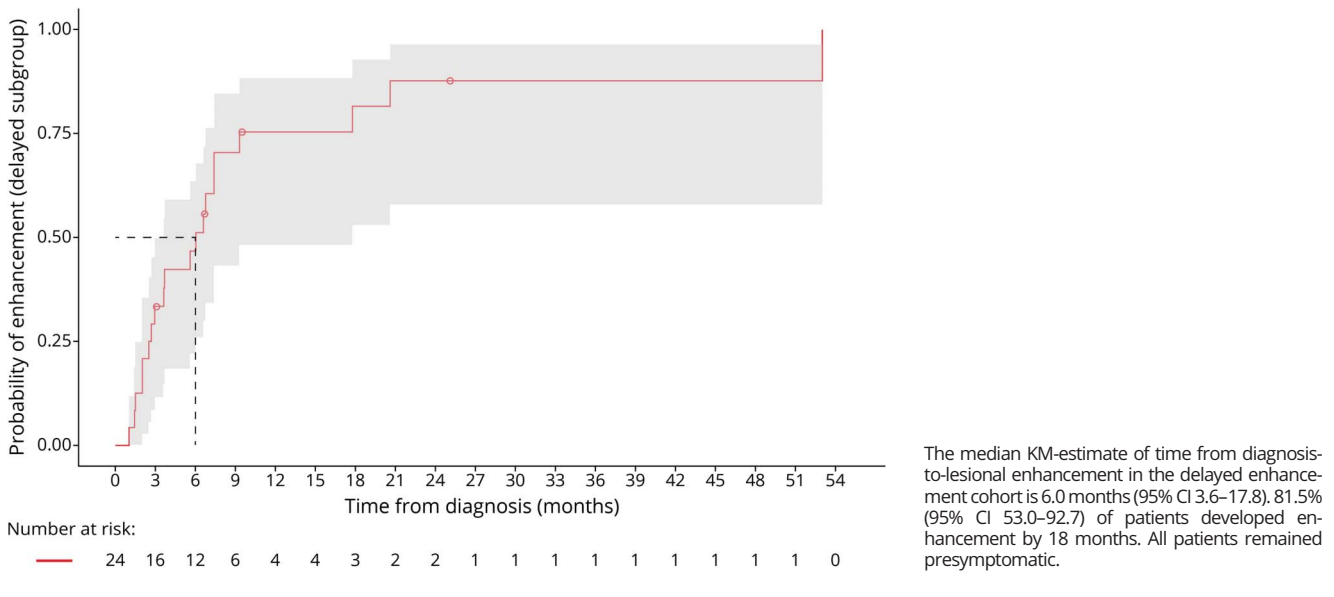
Paired enhancement-to-treatment data were available for 43 patients. The median KM-estimate of time from enhancement-to-treatment is 3.8 months (95% CI 2.8–5.9). All patients were treated by 14.9 months (Figure 4).

Overall treatment data were available for 54 patients. The median KM-estimate of time from *initial* CCALD diagnosis-to-treatment is 7.7 months (95% CI 5.8–11.9 months). One-year and 2-year treatment incidences from *initial* CCALD

Table Clinical and Imaging Scores per End Point

	Diagnosis	Lesion enhancement	Treatment
Age (y)	6.4 (2.4–12.1)	6.5 (3.0–12.7)	7.1 (3.1–15.7)
Neurologic Function Score	0 (0)	0 (0)	0 (0–2)
Loes Score	1.5 (0.5–9.0)	1.0 (0.5–9.5)	2.5 (0.5–11.0)
n	71	44	54

Figure 3 Time From CCALD Diagnosis-to-Enhancement



diagnosis were 66.7% (95% CI 51.4–77.1) and 90.7% (95% CI 78.7–96.0), respectively. Treatment data were not available for 17 patients at this time point.

Subgroup Analyses

Diagnostic LS Less Than or Equal to 1.0

Thirty-five patients had a diagnostic LS ≤ 1.0 . The median age was 5.8 years (2.4–11.5), and all were presymptomatic at diagnosis.

Sixteen of 28 patients with available data were in the delayed enhancement subgroup. The median KM-estimate of time

from diagnosis-to-lesional enhancement is 4.7 months (95% CI 2.7–9.3) (Figure 5). 93.7% (95% CI 58.3–99.1) of patients developed enhancement by 18 months. LS at lesional enhancement was 1.0 (0.5–4), and all patients remained presymptomatic.

At treatment, all patients (100%) with available clinical data ($n = 30$) were presymptomatic, with a median LS of 1.5 (0.5–9.0). Paired enhancement-to-treatment data were available for 28 patients. The median KM-estimate of time from enhancement-to-treatment is 3.8 months

Figure 4 Time From Enhancement-to-Treatment

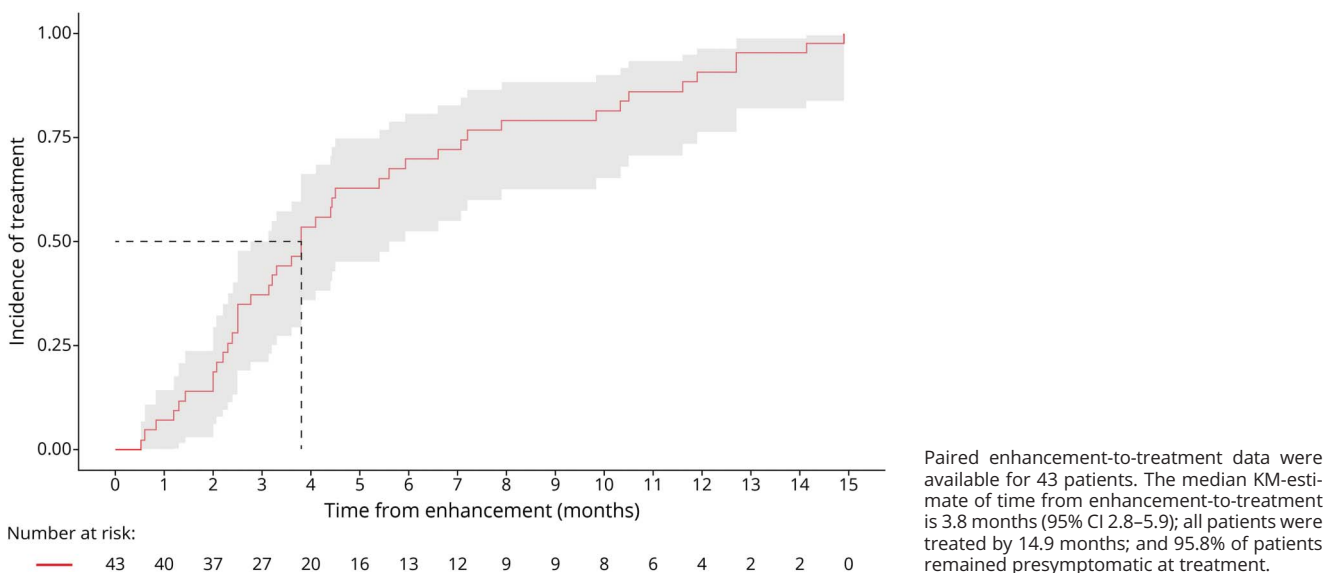
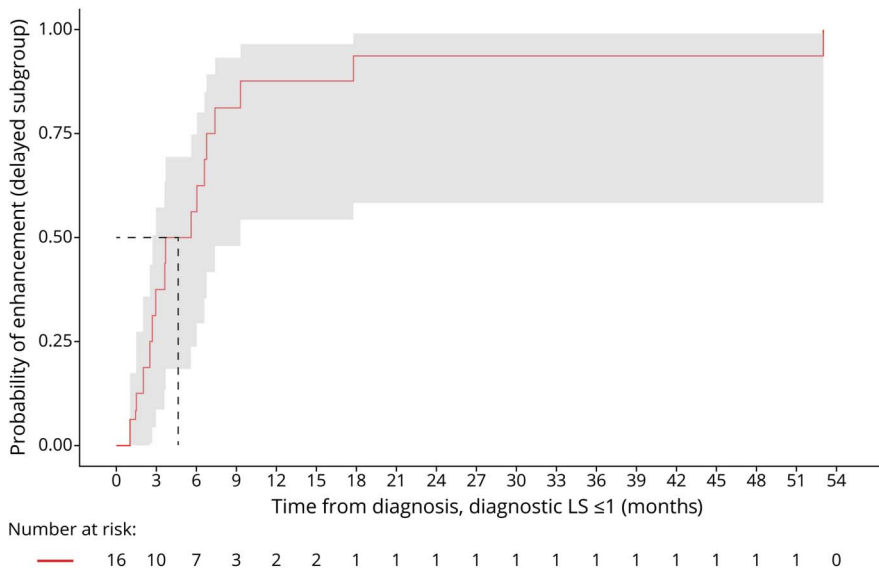


Figure 5 Diagnostic LS < 1.0: Time From CCALD Diagnosis-to-Enhancement



The median KM-estimate of time from diagnosis-to-lesional enhancement in the delayed enhancement cohort is 4.7 months (95% CI 2.7–9.3). 93.7% (95% CI 58.3–99.1) of patients developed enhancement by 18 months. All patients remained presymptomatic. CCALD = childhood cerebral adrenoleukodystrophy.

(95% CI 3.1–7.1). All patients were treated by 12.7 months (Figure 6).

67.3–97.7). Twenty-two (95.7%) patients remained asymptomatic at treatment (NFS = 0 [0–2]).

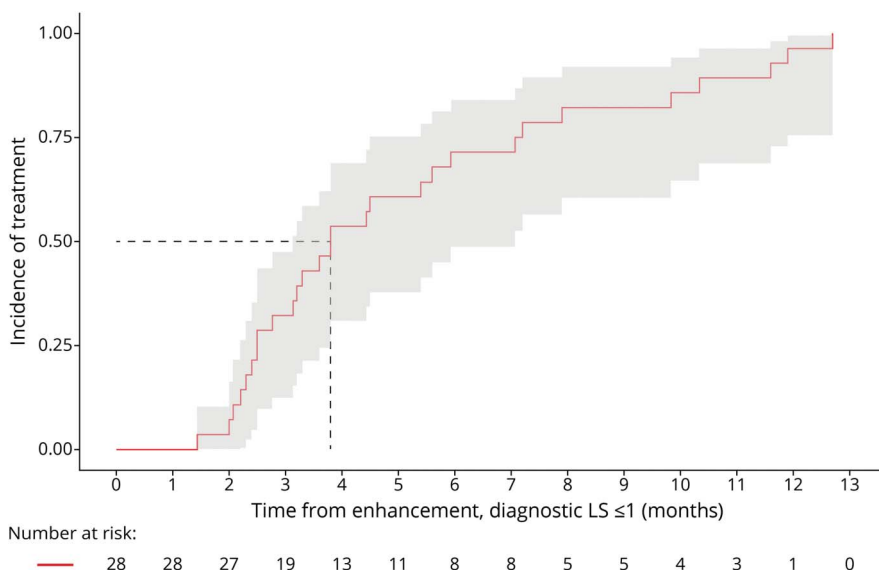
Treatment Performance Over Time

There is an inverse relationship between the year the patients were diagnosed with CCALD (1987–2021) and time from CCALD diagnosis-to-treatment ($\rho = -0.401$, $p = 0.003$). Overall, patients diagnosed with CCALD within the past 5 years were treated with HSCT or gene therapy in a median of 5.8 months (95% CI 3.5–9.7, $n = 23$) from *initial* diagnosis. The incidence of treatment at 12 months is 91.3% (95% CI

Discussion

Childhood cerebral ALD lesions begin small but develop gadolinium enhancement as they enlarge and eventually manifest neurologic symptoms.⁵ Treatment with HSCT or gene therapy is reserved for actively enlarging lesions, which are demarcated by gadolinium enhancement. A delay in treatment

Figure 6 Diagnostic LS ≤ 1.0: Time From Enhancement-to-Treatment



Paired enhancement-to-treatment data were available for 28 patients. The median KM-estimate of time from enhancement-to-treatment is 3.8 months (95% CI 3.1–7.1). All patients were treated by 12.7 months. All patients remained presymptomatic.

initiation allows the lesion to progress further, yielding poorer clinical outcomes.^{8,12,17,27} Understanding the onset, progression, and time to treatment is necessary for optimizing care and designing clinical trials. In our cohort of 71 boys with CCALD, we find that lesions appeared at a median age of 6.4 years, but as early as 2 years of age. Half of the patients displayed lesional enhancement at diagnosis. The other half developed lesional enhancement on continued contrast-enhanced surveillance imaging in 6 months. The time from enhancement-to-treatment was 3.8 months for the whole cohort. Only 2 patients (4.2%) developed symptoms before treatment had begun.

Our previous analysis of mixed presymptomatic and early symptomatic patients suggested a median age of CCALD onset of 7.0.²¹ The younger median age in this study was expected because we restricted our analysis to presymptomatic lesions only. Therefore, the results likely offer a more accurate indication of disease onset, specifically 7 months earlier than the previously published estimate. Furthermore, we aimed to approximate the newborn screening experience by restricting the analysis to presymptomatic patients diagnosed with the earliest lesions ($LS \leq 1.0$). In these cases, the median age of diagnosis was 5.8 years, 1.2 years earlier than the patient cohort in our previous work.

In patients who are diagnosed with an initial nonenhancing CCALD lesion, physicians and families should expect the emergence of lesional enhancement in 50% of patients by 4.7 months if the diagnostic LS was 1.0 or less and by 6.0 months overall. Lesional enhancement is to be expected in 81.5% of patients by 18 months. This supports the recommendation that patients with an identified cerebral lesion should, in parallel to continued contrast-enhanced MRI monitoring, be evaluated and prepared for HSCT or gene therapy to minimize treatment delivery time once lesional enhancement is present.

Importantly, physicians should be aware that enhancement may “flicker on” before developing sustained perilesional inflammation. This was a novel observation in 3 patients in this study captured by close interval follow-up imaging or pretransplant MRI. This radiographic phenomenon has been demonstrated in adults with arrested CALD who developed temporary lesional enhancement, step-wise disease progression, followed by spontaneous remission of contrast enhancement and disease restabilization.^{23,28} A similar observation has been noted in the residual enhancement present on MRI in some patients with CCALD who have received gene therapy.²⁹ The phenomenon of “flickering” lesions bears further study because it may represent oscillations around immune and metabolic homeostasis that could shed new insights on disease pathogenesis and treatment.

Our data suggest that CCALD onset can occur at any time between age 2 and 12 years; capturing presymptomatic CCALD does not necessarily mean capturing patients at a younger age. The lack of a significant mathematical

relationship between diagnostic age, LS at diagnosis, and time-to-detection of lesional enhancement further supports this notion. For lesion distribution, projection fiber involvement was observed at a higher rate than in previously published studies,^{5,7} appearing in 21.1% of all lesions in this cohort. The degree of internal capsular involvement is important to consider at diagnosis because the neurologic examination is sensitive to long-tract pathology, and it may frame clinical expectations given affected patients may be at higher risk for disease progression and posttransplant symptom development, as seen in the 3-year-old patient who became symptomatic in this study.^{30,31}

Akin to the concept of “door-to-needle time,” patients with the earliest evidence of actively inflammatory CCALD should aim to be treated within 4 months from the onset of lesional enhancement, with the welcome expectation that nearly all patients will remain asymptomatic. Neurocognitive outcomes^{13,16} can be maximized if patients are treated with “very low severity” MRI scores (before the MRI exceeds a LS of 2.0). This was observed in the subanalysis of patients with a diagnostic $LS \leq 1.0$, all of whom were treated presymptomatically with a median LS of 1.5.

There are features of CCALD that are patient-specific and not captured by group-level analyses. The rate of disease progression, onset of symptoms, and lesional distribution in the 2 patients who became symptomatic at treatment illustrate this interpatient variability. One boy developed enhancing cerebral disease at age 3 years, with splenial and internal capsular involvement, the latter of which was likely the cause of his hyperreflexia and running difficulty at the time of treatment 5 weeks later. Conversely, while the 26-month time interval from presymptomatic diagnosis to symptomatic treatment of the second patient affected by an isolated pattern 1 lesion indicates less overall disease burden and slower progression, it does highlight the danger in delayed treatment.

Ninety-one percent of patients diagnosed with progressive CCALD within the past 5 years were treated within 1 year. If follow-up contrast-enhanced MRI surveillance continues to reveal nonenhancing cerebral disease with no changes in the LS for more than a year to 18 months from the initial abnormal MRI, especially in an older child (older than 8 years), a diagnosis of arrested CCALD should be considered in the differential diagnosis, serial contrast-enhanced MRI monitoring should continue every 3 months, and treatment should be deferred.^{6,23} It is imperative that physicians do not prematurely diagnose the first signs of early, nonenhancing, demyelination as self-halted CCALD; patients in the delayed enhancement subgroup may initially meet arrested criteria by default. All early-stage lesions must be monitored every 3 months by MRI while the disease declares itself, and the differential diagnosis should only broaden to include spontaneous CCALD remission after a patient is outside of the expected 12–24 months expected treatment window. Novel, advanced imaging techniques, including MR perfusion and

lesion volumetrics, may help to parse out actively progressing vs self-stabilizing lesions at these earliest time points.³²⁻³⁴

Important limitations apply to this study. Although the data are semilongitudinal, not all clinical and imaging variables were available at each time point, most often because of loss to follow-up or unavailability of historical medical records. Because of missing data, we opted for the more statistically conservative approach; we analyzed each of the end points as independent, nonpaired events. The incomplete availability of paired data limited our ability to calculate more robust survival estimates. Some boys early in the study (before 2005) participated in the Lorenzo's Oil (LO) trial. The results suggested that asymptomatic patients treated preventatively with LO may have altered the incidence of CCALD, possibly decreasing the number of patients available for this study. LO has not been shown to alter the course of disease once a cerebral lesion develops. In addition, the results have not been replicated, and the study was not placebo-controlled.²⁶ The time-to-enhancement may be overestimated as not all initial scans were administered with gadolinium. The minimal amount of deidentified data required to perform the planned analyses were collected to promote feasibility of the study while protecting patient confidentiality. The data did not include annotation of which early MRI scans were contrast vs non-contrast-enhanced, thus leading to a potential overestimation to the time-to-enhancement estimate in the delayed enhancement cohort. The potential overestimation of this window may be favorable given all patients remained presymptomatic at this end point. It is important to note that MR sensitivity and overall treatment performance has improved over the course of this study, the effect of which we accounted for by analyzing the subset of patients diagnosed since 2016. Historically (before 2000), time-to-treatment was longer in presymptomatic patients because of the high mortality of HSCT, which introduced significant pause on the part of the families deciding to move forward with the procedure. Collectively, these limitations highlight the need for these results to be validated by analyzing other independent ALD cohorts. The presence of missing data also underscores the importance of a prospective ALD natural history study to more clearly define the longitudinal timing of early-stage CCALD onset, progression, divergence to arrested disease, clinical symptomatology, and treatment.

The results of this study provide insight into the presymptomatic "window of opportunity" by clarifying the timing of CCALD lesion development, and by quantifying the time frame from the detection of perilesional inflammation-to-treatment of boys diagnosed with presymptomatic CCALD. Our data will help optimize MRI surveillance, the timing and clinical expectations for treatment, and has the potential to frame preventative and early treatment trials for this devastating disease of childhood.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Eric J. Mallack, MD	Weill Cornell Medicine, New York	Conceptualized the study, completed the data acquisition, carried out the data analyses, drafted and completed the manuscript, and critically reviewed and revised the manuscript.

Continued

Appendix (continued)

Name	Location	Contribution
Keith Van Haren, MD	Stanford University School of Medicine, California	Completed the data acquisition, updated the data analysis, critically reviewed and revised the manuscript, and critically reviewed intellectual content.
Anna Torrey, BS	Weill Cornell Medicine, New York	Completed the data acquisition, carried out the data analyses, and drafted and completed the manuscript.
Stephanie van de Stadt, MD	Amsterdam University Medical Center, The Netherlands	Completed data acquisition, carried out initial analyses, and critically reviewed and revised the manuscript.
Marc Engelen, MD, PhD	Amsterdam University Medical Center, The Netherlands	Supervised the data collection, critically reviewed and revised the manuscript, and critically reviewed intellectual content.
Gerald V. Raymond, MD	Kennedy Krieger Institute, Maryland	Supervised the data collection, critically reviewed and revised the manuscript, and critically reviewed intellectual content.
Ali S. Fatemi, MD	Kennedy Krieger Institute, Maryland	Supervised the data collection, updated the data analysis, critically reviewed and revised the manuscript, and critically reviewed intellectual content.
Florian S. Eichler, MD	Massachusetts General Hospital, Massachusetts	Supervised the data collection, updated the data analysis, critically reviewed and revised the manuscript, and critically reviewed intellectual content.

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