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Intensity of MRI gadolinium enhancement in cerebral adrenoleukodystrophy: a biomarker for inflammation and predictor of outcome following transplant in higher-risk patients

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Abstract

BACKGROUND AND PURPOSE—Outcomes following hematopoietic stem cell transplantation for higher-risk childhood-onset cerebral adrenoleukodystrophy are variable. We explored whether a brain MRI gadolinium intensity scoring system improves prediction of neurologic outcome.

METHODS—A four-point scale of gadolinium intensity relative to the choroid plexus was developed: 0 = no enhancement; 1 = hypo-intense; 2 = iso-intense; 3 = hyper-intense. The scale's inter-observer concordance was assessed on 30 randomly chosen studies. Scores were generated for 64 evaluable patients and compared with cerebrospinal fluid chitotriosidase levels, a known inflammatory marker correlating with outcomes following transplant. For 25 evaluable higher-risk patients (Loes ≥ 10), the gadolinium intensity score was compared with longer-term post-transplant clinical change.

RESULTS—The gadolinium intensity scoring system showed good inter-observer reproducibility (kappa = 0.72). Of 64 evaluable boys, the score positively correlated with average concomitant cerebrospinal fluid chitotriosidase activity in ng/mL/hr: (0), 2,717, n=5; (1), 3,218, n=13; (2), 6,497, n=23; and (3), 12,030, n=23 ($p < 0.01$). For 25 evaluable higher-risk patients, more intense pre-transplant brain MRI gadolinium enhancement predicted greater average loss on the

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adrenoleukodystrophy neurologic function scale following transplant: (0/1), ΔNFS = 4.3, n = 7; (2/3), ΔNFS = 10.4, n = 18 (p = 0.05).

CONCLUSION—Gadolinium enhancement intensity on brain MRI can be scored simply and reproducibly for cerebral adrenoleukodystrophy. Enhancement score significantly correlates with chitotriosidase. In boys with higher-risk cerebral disease (Loes ≥ 10), enhancement score itself predicts neurologic outcome following treatment. Such data may help to guide treatment decisions for clinicians and families.

Introduction

Adrenoleukodystrophy (ALD) is an X-linked peroxisomal disorder affecting approximately 1 in 21,000 males. Mediated by elevated concentrations of very long chain fatty acids, disease may manifest as central nervous system demyelination, primary hypoadrenalism, and/or primary hypogonadism. The disease results from pathogenic mutations in the peroxisomal transporter *ABCD1* gene, but genotype does not predict the presentation and different presentations may occur within the same family.[1, 2]

In 35% of affected males, cerebral involvement (cALD) begins in childhood. This devastating phenotype is characterized by rapidly progressive central nervous demyelination and, if untreated, usually death within years of onset of clinical signs and symptoms.[3] Post-mortem analyses of affected brains have implicated mononuclear inflammatory mechanisms.[4–6] Radiographic changes generally precede clinical neurologic disease by several years in childhood cALD and are characterized by symmetric, expanding white matter lesions.[7] Consistent with known neuro-inflammatory histopathology, gadolinium enhancement is typically observed near the leading edge of active demyelination and, when present, strongly predicts disease progression.[8, 9] The Loes cALD brain MRI severity scale is commonly used to quantify radiographic disease burden with adrenoleukodystrophy. Increasing Loes scores denote accumulating white matter disease and atrophy in defined neuro-anatomic or functional regions: periventricular/subcortical areas (parieto-occipital, anterior-temporal, and frontal), corpus callosum, visual pathways, auditory pathways, frontopontine-corticospinal projection fibers (internal capsule and brain stem), basal ganglia, cerebellum, and anterior thalamus. For ALD patients with no cerebral involvement the Loes is by definition zero, while maximal cerebral involvement on the scale (Loes = 34) correlates with profound neurologic impairment.[10]

Although experimental gene therapy trials are currently underway, allogeneic hematopoietic stem cell transplantation (HSCT) remains standard therapy to arrest cerebral disease progression in cALD.[3] Importantly, long-term functional outcome analyses have demonstrated critical dependence upon cerebral white matter disease burden as measured by the Loes score at the time of transplant.[11] Most patients with Loes < 10 are absent signs of cerebral disease as measured on the ALD Neurologic Function Scale (NFS, Figure 1)[12] and are considered strongly for HSCT. For these standard-risk cALD patients (Loes < 10 at HSCT), gross neurologic function following transplantation nearly uniformly remains the same on the NFS. However, outcomes after transplant for higher-risk disease (Loes ≥ 10 at HSCT) are considerably more difficult to prognosticate and range from mild clinical

progression to profound devastation.[13] For such higher-risk patients, the absolute pre-transplant Loes score alone does not predict neurologic outcome.

Despite efforts for early detection, many boys still arrive at ALD diagnosis because of neurologic impairment from higher-risk cALD (Loes ≥ 10). In these cases, clinicians and families face difficult decisions regarding the use of HSCT, a procedure that carries significant risk of injury and mortality.[14] Therefore, additional prognostic indicators of likely benefit from HSCT in these higher-risk cALD patients who already demonstrate extensive cerebral white matter disease burden at diagnosis are sought.

In previous reports, a strong correlation between pre-transplant chitotriosidase enzyme activity (CHIT, elaborated by activated monocytes) in plasma and cerebrospinal fluid (CSF) and clinical neurologic change at 1 year following HSCT for cALD has been observed.[15] In that analysis, higher CSF CHIT in the pre-transplant setting strongly correlated with clinical neurologic worsening for a non-stratified cALD cohort (standard and higher-risk patients combined).

We have anecdotally observed a possible correlation between the intensity of gadolinium enhancement on pre-HSCT brain MRI and clinical neurologic outcomes following HSCT in higher-risk cALD (Loes ≥ 10). In this single-institution study, we establish a simple gadolinium intensity scoring (GIS) system for cALD brain MRI and apply it to a large patient cohort. We explore the reproducibility of the GIS and its correlation with concomitant CSF CHIT. Finally, we analyze the pre-transplant GIS predictive value for post-transplant neurologic outcomes in higher-risk cALD.

Methods

Cohort Identification and Cerebrospinal Fluid Chitotriosidase Activity Determination

All patients confirmed to have ALD by diagnostic plasma very long chain fatty acid profile and who underwent evaluation at our center after January 1, 2000 were considered for this retrospective study. CSF CHIT activity and CHIT genotypes were determined by methods previously described.[15]

As one aim of our analysis was to assess for a correlation between GIS and CSF CHIT in cALD regardless of how limited or extensive white matter disease may be, *all* patients with cALD, regardless of Loes score, were included for analysis of GIS and CSF CHIT correlation if they had (1) an untreated MRI evaluable for GIS (pre-transplant, if the patient proceeded to HSCT), and (2) concomitant CSF CHIT data. For patients genotypically determined to be heterozygous *CHIT* null ($CHIT^{WT}/CHIT^{0}$, seen in approximately 35% of the general population), CSF CHIT activity reported for this study was set to twice that measured in assay. Patients were excluded for analysis of GIS and CSF CHIT correlation if they (1) were genotypically homozygous *CHIT* null ($CHIT^{0}/CHIT^{0}$, seen in approximately 5% of the general population), as these patients are not capable of producing enzyme or (2) did not demonstrate MRI evidence of cerebral disease (Loes = 0).

As previous reports have shown *standard-risk* cALD patients (Loes < 10 at the time of HSCT) to demonstrate no-to-minimal worsening in post-transplant, general clinical neurologic function[13], only *higher-risk* cALD patients (Loes ≥ 10 at the time of transplant) were considered for retrospective analysis of correlation between pre-transplant GIS and neurologic function outcomes post-transplant. These higher-risk patients were included in this study if (1) a pre-transplant brain MRI was evaluable for GIS; (2) pre-transplant Loes score was ≥ 10; and (3) robust donor hematopoietic engraftment (≥ 80%) was achieved following transplant. Patients were excluded if death resulted from transplant-related complications.

All transplanted patients were treated on protocols approved by the Institutional Review Board and following the provision of informed consent. For each patient, the best available allograft according to standard institutional guidelines was chosen. Transplant conditioning regimen was dependent upon the appropriate protocol available to the patient at the time of transplant. Antimicrobial prophylaxis and therapy, graft-versus-host disease prophylaxis, and blood product supportive care were by standard institutional guidelines.

ALD MRI Severity (Loes) Score and Gadolinium Intensity Score (GIS) Assignment

Brain MRI studies included in this analysis were prospectively assigned a severity score according to the Loes system by a single neuro-radiologist (DN) who was blinded to CHIT data and neurologic outcomes.[10]

Gadolinium intensity scores (GIS) were determined from 3D-T1W MPRAGE (TR: 1,900 ms; TE: 2.19 ms; TI: 900 ms; 1 average; flip angle: 9 degrees; slice thickness: 0.9 mm; voxel size: 0.9 × 0.9 × 0.9 mm; matrix: 256 × 256) images obtained approximately 5 minutes following intravenous (IV) dosing of either Magnevist (meglumine gadopentetate) 0.1 mmol/kg or Gadavist (gadobutrol) 0.05 mmol/kg (Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ 07981).

As gadolinium enhancement intensity may vary due to inter-scan differences in timing of the IV contrast bolus, we developed the GIS to be internally controlled. Each brain MRI was assigned a GIS as follows: 0 = no contrast enhancement; 1 = maximal lesion enhancement less than that of the choroid plexus; 2 = maximal lesion enhancement of equal intensity to the choroid plexus; 3 = maximal lesion enhancement more intense than the choroid plexus (Figure 2). All GIS used for analysis were assigned by a single neuroradiologist (DN) who was blinded to CHIT data and neurologic outcomes.

Fleiss's kappa was used to assess inter-rater agreement among three neuroradiologists (DN, JR, RG) on 30 randomly selected scans. Good inter-observer reliability was observed (kappa = 0.72).[16]

Neurologic Function Scale Score Assignment

For transplanted higher-risk cALD patients (Loes ≥ 10 at HSCT), clinical cerebral disease severity was scored immediately before HSCT and at the latest post-transplant follow-up using the ALD NFS (Figure 1).[12] NFS assignment was performed from retrospective review of clinical notes by a single investigator (WM) who was blinded to radiographic GIS, Loes

and CHIT data. Change in NFS (ΔNFS) was defined as the difference between the NFS at most recent follow-up and the baseline NFS obtained immediately prior to HSCT. For patients who died of cALD disease progression following HSCT, the most recent NFS was set to maximum (25) at the time of death.

Study Objectives and Statistical Analyses

The main objective of this retrospective cohort study was to determine in all evaluable cALD patients if brain MRI gadolinium intensity correlates with CSF CHIT, an inflammatory biomarker shown to associate with neurologic function at 1 year following transplant for cALD. A secondary objective was to determine if pre-transplant GIS correlates with long-term change in neurologic function (ΔNFS) in higher-risk cALD patients (Loes ≥ 10) undergoing HSCT.

Comparisons of mean CSF CHIT activity levels across each cALD GIS score were made by the Kruskal-Wallis test. Comparison of mean CSF CHIT activity by GIS group in higher-risk cALD patients (Loes ≥ 10) was performed with the t-test using the Welch correction for disparate variance. Comparison of change in NFS score (ΔNFS) by GIS group in higher-risk cALD (Loes ≥ 10) patients was performed with the t-test.

Results

Brain MRI Gadolinium Intensity Score Correlates Strongly with CSF Chitotriosidase Activity in cALD

Sixty-four boys with cALD were evaluable for simultaneous CSF CHIT and brain MRI GIS. Very few patients (n=5) demonstrated no gadolinium enhancement (GIS=0). The remaining cohort (n=59) was distributed relatively equally among non-zero GIS. For the entire group, mean CSF CHIT varied significantly between GIS cohorts (Figure 3). GIS, mean CSF CHIT activity (ng/mL/hr), and number of patients observed were as follows: GIS(0), 2,717, n=5; GIS(1), 3,218, n=13; GIS(2), 6,497, n=23; and GIS(3), 12,030, n=23 ($p < 0.01$, difference in mean CHIT across GIS groups).

When considering higher-risk cALD patients only (Loes ≥ 10), CSF CHIT varied significantly by GIS (Figure 3). Because of low patient numbers in this cohort subset, a binary GIS status was assigned. Patients with low GIS (1/2, n=6) demonstrated a mean CHIT of 4,844 ng/mL/hr (95% CI, 2,429 to 7,393), while those with high GIS (2/3, n=34) showed a mean CHIT of 11,892 ng/mL/hr (95% CI, 8,461 to 15,322; $p < 0.01$, difference in mean CHIT).

Pre-transplant Brain MRI Gadolinium Intensity Score Correlates with Longer-Term Clinical Neurologic Outcome Following HSCT in Higher-Risk cALD

Twenty-five patients with higher-risk cALD (Loes ≥ 10 at HSCT) and near complete donor hematopoietic engraftment following HSCT (> 80% at most recent follow-up) were evaluable for long-term change in neurologic function (ΔNFS) based on pre-transplant brain MRI GIS (Figure 4). Seven patients with low GIS (0/1) demonstrated a mean ΔNFS of 4.3 at an average post-transplant follow-up of 3 years. Eighteen patients with high GIS (2/3)

experienced a mean ΔNFS of 10.4 at an average post-transplant follow up of 1 year, 10 months ($p = 0.05$, difference in mean ΔNFS).

The distribution of transplant, demographic, and Loes characteristics between the two groups are shown in Table 1.

Discussion

Currently, allogeneic hematopoietic stem cell transplantation is considered the best treatment for "standard-risk" childhood cerebral adrenoleukodystrophy (Loes brain MRI severity score < 10).[3, 13, 17] In these children with relatively low-level cerebral white matter involvement at the time of HSCT, gross neurologic function on the ALD NFS is generally normal before transplantation and remains largely unchanged after. However, a significant proportion of cALD patients present at diagnosis with advanced, often-symptomatic cerebral disease. Owing to greater white matter involvement (Loes ≥ 10), these cALD patients are considered "higher-risk" for poor neurologic outcomes after transplant.

In a recent analysis, 30 consecutive higher-risk patients (Loes ≥ 10) were reported to suffer a median ΔNFS of 7.5 (IQR, 4 to 19; range, 0 to 23) when analyzed at a median 2.1 years after HSCT. Such highly variable and unpredictable neurologic outcomes (ranging from mild, if any, changes to significant neurologic impairment) make for difficult decisions by both clinicians and families, especially as no other effective therapies for higher-risk cALD currently exist. And while large analyses have shown consistently favorable neurologic outcomes for patients with a pre-transplant Loes < 10, the absolute pre-HSCT Loes score within the higher-risk cALD group (pre-transplant Loes ≥ 10) has not alone proved prognostic.[13] Therefore, additional predictive biomarkers for this challenging patient sub-set are sought.

Recently, a tight correlation between pre-transplant CHIT activity in CSF and neurologic outcomes at 1 year following HSCT for all cALD has been reported.[15] As CHIT is elaborated by activated monocytes and macrophages, this marker may quantify active neuro-inflammation in a cALD patient. However, CHIT assay is not readily available to most clinicians when assessing boys with cALD. Furthermore, baseline CHIT has not yet been shown within the higher-risk cALD subset to be a clear predictor of neurologic function after HSCT.

Radiographic strategies for the quantification of neuro-inflammation are limited. While the Loes score is an objective measurement of brain regions affected by demyelination, it does not reflect volume of brain involved, nor does it quantify contrast enhancement. Practical volumetric analysis of affected white matter or of areas involved by inflammation is not easily performed with standard clinical PACS from most vendors. Therefore, we developed a simple scoring system based on the maximal intensity of enhancement observed on each cALD brain MRI, positing a correlation between the degree of enhancement and active neuro-inflammation. Because observer judgment of MRI gadolinium enhancement intensity is fundamentally relative, our system incorporates intra-scan intensity in the highly vascular

choroid plexus as a normalizing reference. Indeed, we found the scoring system to have high inter-observer reproducibility among neuroradiologists.

Using this scale, we showed that higher gadolinium enhancement intensity scores on the untreated cALD brain MRI positively correlate with concomitant CSF CHIT. Furthermore, for patients with higher-risk cALD at the time of HSCT (Loes ≥ 10), we observe an association between higher pre-transplant GIS scores and worse longer-term neurologic functional outcomes. There were relatively fewer higher-risk cALD patients (Loes ≥ 10) in our evaluable cohort who had lower GIS status at baseline (4% with GIS=0 and 24% with GIS=1). However, our findings suggest significantly better neurologic outcomes for this group deemed higher-risk by Loes score (ΔNFS of only 4.3, versus ΔNFS of 10.4 for higher-risk patients with GIS=2/3) at a long-term post-transplant follow-up. Though the mechanism of action of HSCT for cALD is not well understood, it may in part exert its desired effect (arresting further myelin loss) by quelling neuro-inflammation. In the higher-risk cALD patient (Loes ≥ 10), the baseline absolute Loes score - which tallies discreet regions within the cerebrum, brainstem and cerebellum with radiographically evident demyelination - has not been observed to independently correlate with post-transplant neurologic outcome. But the Loes system neither accounts for nor attempts to quantify radiographic evidence of neuro-inflammation. In fact, among evaluable higher-risk cALD patients in this current analysis (Loes ≥ 10), gadolinium enhancement intensity as measured by GIS did not correlate with absolute Loes score (data not shown). Therefore, biomarkers that do address this component to active cALD may add prognostic value.

A hindrance to better understanding HSCT for cALD is the relative rarity of the disorder. Though this cohort is considered large in the field, our study is limited due to few evaluable patients. In particular, confidence in the utility of the pre-transplant GIS to predict neurologic outcomes following HSCT for higher-risk cALD (Loes ≥ 10) would be greater if more of such patients were evaluable. Ultimately, a matrix of various “measures” of cerebral disease burden prior to HSCT (clinical, neuropsychologic, tissue biomarkers, Loes severity, and gadolinium intensity status) may better predict likely longer-term outcomes for this challenging cALD population.

Conclusions

Brain MRI gadolinium enhancement in cALD can be quantified with a simple, reproducible scoring system. When applied to MRI studies of untreated boys, the gadolinium intensity score shows strong positive correlation with the activity of cerebrospinal chitotriosidase, an enzyme elaborated by activated monocytes and previously shown to correlate with neurologic function at 1 year post-transplant in all cALD patients undergoing HSCT. In higher-risk cALD (Loes ≥ 10), a subset for whom prediction of neurologic outcomes following HSCT has been difficult, the baseline brain MRI gadolinium intensity status appears to significantly predict long-term neurologic functional change. Although this study was performed using a dedicated 3T MRI protocol with fixed T1-WI parameters, we believe this method will likely yield useful information regardless of scanner manufacturer, field strength, or sequence parameters. These findings may help to inform clinician and parental decision making for higher-risk cALD patients who seek transplant intervention.

Abbreviations

cALD	cerebral adrenoleukodystrophy
CHIT	chitotriosidase
CSF	cerebrospinal fluid
GIS	brain MRI gadolinium intensity scale score
HSCT	hematopoietic stem cell transplant
NFS	adrenoleukodystrophy neurological function scale score

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Hearing/auditory processing problems	**1**
Aphasia/apraxia	**1**
Loss of communication	**3**
Vision impairment/fields cut	1
Cortical blindness	2
Swallowing difficulty or other central nervous system dysfunction	**2**
Tube feeding	**2**
Running difficulties/hyperreflexia	1
Walking difficulties/spasticity/spastic gait (no assistance)	1
Spastic gait (needs assistance)	2
Wheelchair required	2
No voluntary movement	3
Episodes of urinary or fecal incontinency	**1**
Total urinary or fecal incontinency	**2**
Nonfebrile seizures	1
Possible Total	**25**

FIG 1.

The cerebral adrenoleukodystrophy Neurologic Function Scale (NFS) used to evaluate gross clinical neurologic status for the higher-risk cALD cohort pre-transplant and at most recent post-transplant follow-up. Note that a score of zero denotes absence of clinical signs of cerebral disease. Maximal signs within a domain score the total of all grades within that domain (for example, a patient with “total urinary or fecal incontinency” scores 3, for the sum of episodes of incontinency [1] and total incontinency [2].)

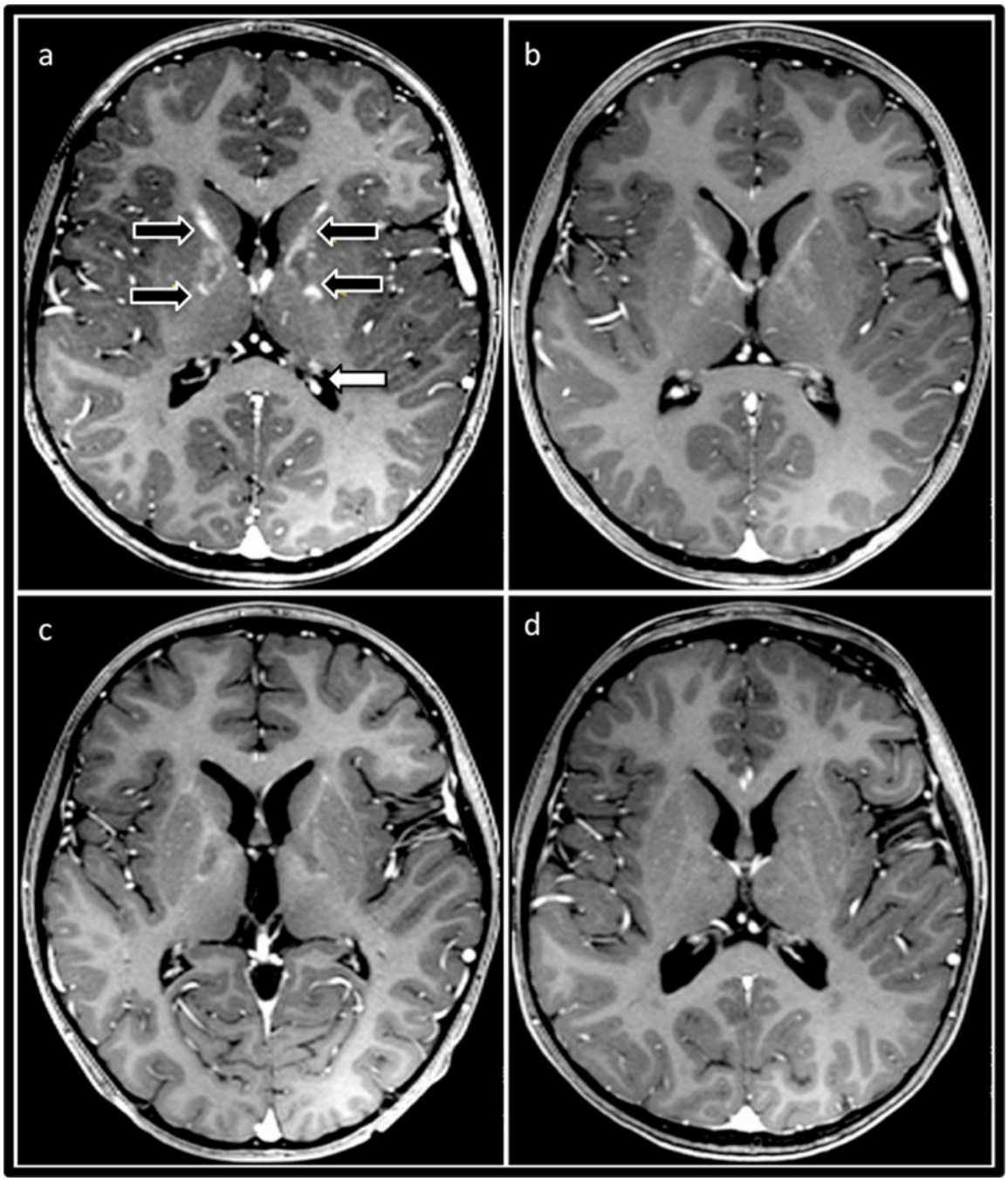

FIG 2.

A gadolinium intensity scoring (GIS) system for cerebral adrenoleukodystrophy demonstrated by successive post-contrast T1-WI of a 7 year-old male with ALD primarily involving the internal capsule. This patient exhibits all 4 grades of GIS, from initial intense contrast enhancement progressing to non-enhancement. 1a, Pre-HSCT MRI demonstrates GIS = 3 in the internal capsules (black arrows) with maximal lesion enhancement hyper-intense to the choroid plexus (white arrow). 1b, 30 days post-HSCT, GIS =2, as maximal lesion enhancement equal to the choroid plexus is observed. 1c, Later, MRI exhibits GIS = 1

with maximal lesion enhancement hypo-intense to the choroid plexus. 1d, 90 days after successful HSCT, resolution of contrast enhancement is seen (GIS = 0).

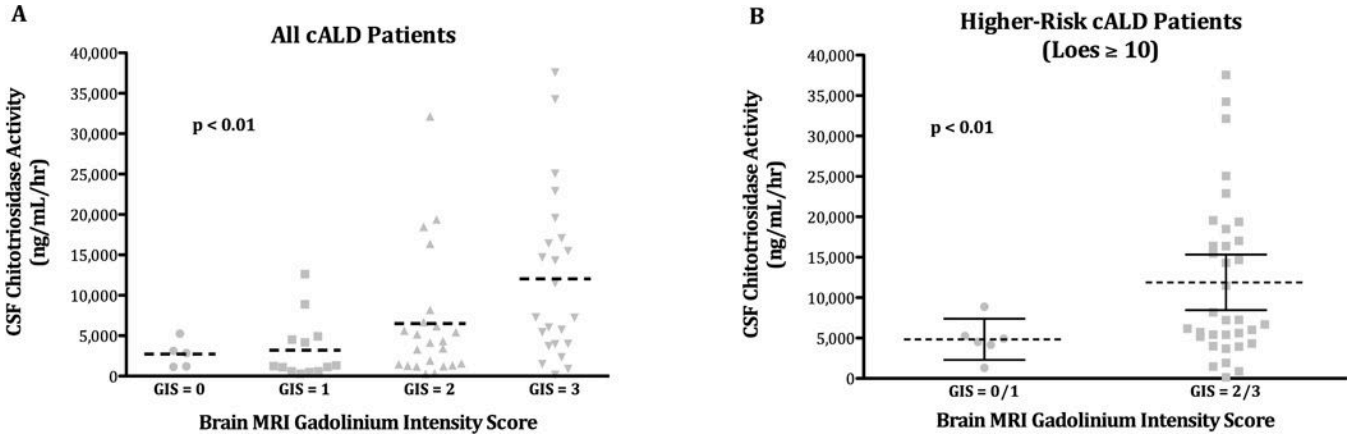

FIG 3.

CSF chitotriosidase activity correlates with brain MRI gadolinium intensity score in cALD. A, Mean value of CSF CHIT activity (dashed line) by GIS for the entire evaluable cALD cohort (n = 64). B, Mean value of CSF CHIT activity (dashed line) and 95% confidence intervals (solid bars) by GIS for patients with higher-risk cALD (Loes ≥ 10; n = 40).

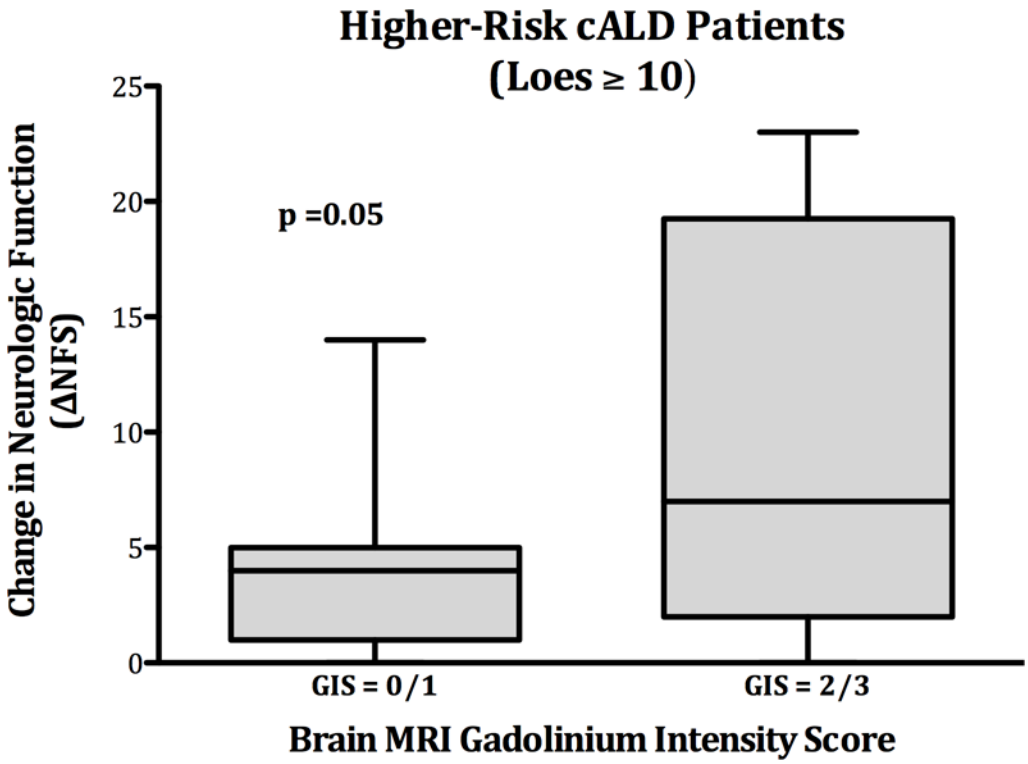

FIG 4.

Change in Neurologic Function Score after HSCT correlates with pre-transplant MRI Gadolinium Intensity Score in higher-risk cALD. ΔNFS by pre-transplant brain MRI GIS status for patients with higher-risk cALD (Loes ≥ 10 at transplant). Seven patients had low GIS status (0/1) while 18 had high GIS status (2/3) on pre-transplant MRI. Solid rectangles show 1st quartile (bottom), median (mid-line) and 3rd quartile (top) results; whiskers define range.

Table 1

Demographic, transplant and Loes characteristics in higher-risk cALD patients (Loes ≥ 10) analyzed for neurologic function change by pre-transplant gadolinium intensity score.

	GIS 0/1 (n = 7)	GIS 2/3 (n = 18)	Difference (95% CI)
Age at HSCT (years)			
Mean	10.1	9.0	1.2 (−1.9, 4.2)
IQR	8.1 – 13.3	6.8 – 10.0	
Pre-HSCT Loes			
Mean	12.6	14.0	−1.5 (−3.3, 0.4)
IQR	11 – 14	11 – 16	
Donor Chimerism (%)			
Mean	98.7	97.1	1.6 (−2.1, 5.3)
IQR	100 – 100	92 – 100	

GIS = gadolinium intensity score on brain MRI; CI = confidence interval; HSCT = hematopoietic stem cell transplantation; IQR = inter-quartile range; Donor chimerism reflects percent donor hematopoietic engraftment at most recent follow up.