Childhood Cerebral Adrenoleukodystrophy: MR Perfusion Measurements and Their Use in Predicting Clinical Outcome after Hematopoietic Stem Cell Transplantation


AJNR Am J Neuroradiol 2016, 37 (9) 1713-1720
doi: https://doi.org/10.3174/ajnr.A4773
http://www.ajnr.org/content/37/9/1713
Abstract

BACKGROUND AND PURPOSE: MR perfusion has shown abnormalities of affected WM in cerebral X-linked adrenoleukodystrophy, but serial data is needed to explore the import of such findings after hematopoietic stem cell transplantation. Our aim was to prospectively measure MR perfusion parameters in patients with cerebral adrenoleukodystrophy pre- and post-hematopoietic stem cell transplantation, and to correlate those measurements with clinical outcome.

MATERIALS AND METHODS: Ten patients with cerebral adrenoleukodystrophy prospectively underwent DSC–MR perfusion imaging at <45 days pre-[baseline], 30–60 days post-, and 1 year post-hematopoietic stem cell transplantation. MR perfusion measurements in the 10 patients and 8 controls were obtained from the parieto-occipital WM, splenium of the corpus callosum, leading enhancing edge, and normal–appearing frontal white matter. MR imaging severity scores and clinical neurologic function and neurocognitive scores were also obtained. MR perfusion values were analyzed in the patients with cerebral adrenoleukodystrophy at each time point and compared with those in controls. Correlations were calculated between the pre-hematopoietic stem cell transplantation MR perfusion values and 1-year clinical scores, with P value adjustment for multiple comparisons.

RESULTS: At baseline in patients with cerebral adrenoleukodystrophy, both relative CBV and relative CBF within the splenium of the corpus callosum and parieto-occipital WM significantly differed from those in controls (P = .005–.031) and remained so 1 year post-hematopoietic stem cell transplantation (P = .003–.005). Meanwhile, no MR perfusion parameter within the leading enhancing edge differed significantly from that in controls at baseline or at 1 year (P = .074–.999) or significantly changed by 1 year post-hematopoietic stem cell transplantation (P = .342–.887). Baseline Loes scores correlated with 1-year clinical neurologic function (r = 0.813, P < .0001), while splenium of the corpus callosum relative CBV also significantly correlated with 1-year neurologic function scale and the neurocognitive full-scale intelligence quotient and performance intelligence quotient scores (r = −0.730–0.815, P = .007–.038).

CONCLUSIONS: Leading enhancing edge measurements likely remain normal post-hematopoietic stem cell transplantation in cerebral adrenoleukodystrophy, suggesting local disease stabilization. Meanwhile, parieto-occipital WM and splenium of the corpus callosum relative CBV and relative CBF values worsened; this change signified irreversible injury. Baseline splenium of the corpus callosum relative CBV may predict clinical outcomes following hematopoietic stem cell transplantation.

Abbreviations: ALD = adrenoleukodystrophy; cALD = cerebral X-linked adrenoleukodystrophy; HSCT = hematopoietic stem cell transplantation; K2 = the coefficient obtained by leakage correction of the dynamic bolus; LEE = leading edge of enhancement; MRP = MR perfusion; NAFWM = normal-appearing frontal white matter; PH = peak height; POWM = parieto-occipital white matter; r = relative; SCC = splenium of the corpus callosum.
tion, which is the prominent histologic finding in untreated cALD. Most important, those with less cerebral disease are more likely to benefit from HSCT; thus, timely HSCT is critical.\textsuperscript{6-10}

MR imaging of cALD is vital in predicting disease course and outcomes. The Loes MR imaging severity score, which quantifies the burden of WM disease, correlates with survival and neurologic outcomes after HSCT.\textsuperscript{6-10} The extent of enhancement on postcontrast T1WI, particularly the leading edge of enhancement (LEE), predicts disease progression in untreated cALD, suggesting that blood-brain barrier dysfunction plays a role in cALD.\textsuperscript{3,11,12} Thus, monitoring the LEE and noting that it is halted may be important in defining treatment response.

DSC–MR perfusion parameters such as relative CBV (rCBV), relative CBF (rCBF), relative TTP (rTTP), relative peak height (rPH), and dynamic leakage correction coefficient (K2) can reflect the pathophysiology of various disorders.\textsuperscript{12-17} Elevated CBV reflects high capillary permeability, while low CBV suggests irreversibly injured tissue.\textsuperscript{12-17} CBF reflects tissue perfusion, being increased in high-grade tumors or inflammation, while TTP elevation indicates a delay in perfusion.\textsuperscript{12-17} Peak height is the signal-intensity change from the baseline of a dynamic enhancement curve, while K2 is the coefficient obtained by leakage correction of the dynamic bolus, reflecting permeability at sites of blood-brain barrier injury.\textsuperscript{14,17}

Scant literature exists regarding MRP parameters in cALD at baseline or how they change following HSCT; 1 sole study of 8 patients noted low rCBV within the core of nonenhancing parietal-occipital white matter (POWM) at baseline, while within the LEE rCBV was preserved.\textsuperscript{12} However, other MRP parameters should be explored, and the prognostic impact of baseline (pre-HSCT) regional DSC-MRP parameters on outcome is of primary importance. Thus, according to these limited prior data, the hypothesis of this study was that MRP parameters, in particular rCBV, would be abnormal in the POWM and perhaps the splenium of the corpus callosum, compared with these parameters in controls, while perfusion within the LEE would be preserved following successful HSCT. Hence, the aims of this study were the following: 1) to determine whether MRP parameters at baseline in various regions of the cALD-affected brain differ from those of controls, 2) to describe several MRP parameters on the pre- and post-HSCT cALD MR imaging, and 3) to determine whether any of the measured baseline (pre-HSCT) MRP parameters in various locations correlate with the neurologic outcomes.

**MATERIALS AND METHODS**

**Patient Selection**

Institutional review board approval was obtained for this study; all patients were enrolled after informed consent. MR imaging examinations were performed at 3 time points relative to transplantation: baseline pre-HSCT (<45 days before transplantation), 30–60 days post-HSCT, and 1 year post-HSCT. There was retrospective measurement of the DSC-MRP values. Patients with cALD were included if they met all of the following criteria: 1) biochemical confirmation of ALD, 2) posterior-type cALD variant (the most common type), 3) clinical and neurocognitive evaluations both at baseline and at 1 year, 4) HSCT being performed between January 2010 and January 2014, 5) younger than 18 years of age and, 6) each MR imaging study adequate for the MRP evaluation (Fig 1). Eight male controls were assessed for DSC-MRP values. Controls lacked any cerebral abnormality on MR imaging (which was typically performed to evaluate the skull base or upper neck), had no previous radiation or chemotherapy, and were matched to the ages of patients with cALD at pre-HSCT (baseline) MR imaging.

**MR Imaging Acquisition Technique**

The 3T MR imaging protocol included FLAIR, precontrast 3D T1WI, and postcontrast 3D T1WI. Noncontrast 3D T1WI, necessary for coregistration, used an MPRAGE sequence: TR/TE/NEX/FOV/parallel factor, 1810/3.5 ms/1/230 mm/1.8. For postcontrast 3D T1WI, an intravenous 0.1-mmol/kg of body weight–based dose of gadopentetate dimeglumine (Magnevist; Bayer Healthcare Pharmaceuticals, Wayne, New Jersey) was administered at 4 mL/s for a 10-mL maximum dose (Figs 2–4). The echo-planar DSC-MRP parameters were the following: TR/TE/NEX/FOV/parallel factor, 1500/43 ms/1/230 mm/0.9. For postcontrast 3D T1WI sequence was identical to that of the noncontrast 3D T1WI, being initiated at approximately 10 minutes after the contrast injection.

**MRP Postprocessing and Review**

The postprocessing of 38 total DSC-MRP examinations (10 patients with cALD with 3 time points each; 8 controls with 1 study each) was retrospectively processed on a DynaSuite Neuro MR Workstation (Invivo, Gainesville, Florida) by a staff neuroradiologist (A.M.M., with >10 years’ experience in pediatric neuroimaging) who was blinded to the clinical data. The noncontrast 3D T1WI and FLAIR images were automatically coregistered with the DSC-MRP maps by the postprocessing software and were confirmed visually, with both a neuroradiology fellow and radiology
residents present to aid in confirming the adequacy of the coregistration, the presence/absence of contrast enhancement, and the ROI site. Freehand ROIs of ≥5-mm diameter were measured centrally within the normal-appearing frontal white matter (NAFWM) and within 3 affected sites: the POWM, centrally within the splenium of the corpus callosum (SCC), and the visibly enhancing LEE (such enhancing regions occurred within areas of FLAIR abnormality in either the POWM or SCC) as demonstrated in Figs 2–4. At least 3 ROIs were measured at each site, and the mean was recorded; if lesions were bilateral, the mean of 6 ROIs (3 ROIs on each side) was used. In controls, normal POWM was substituted for the LEE measurement because no enhancement was present. Notably, LEE lesions being either bilateral, unilateral, or midline prevented a side-to-side comparison of MRP values and thus necessitated the incorporation of measurements for both sides for a conglomerate mean of at least 3 MRP parameter values.

After ROI placement, leakage-corrected CBV, CBF, TTP, and K2 maps were automatically generated in patients and controls, while PH was calculated by manual analysis of the dynamic contrast curve (Fig 2). Regarding the LEE, because enhancement typically resolves following HSCT for cALD, the post-HSCT MR images were automatically coregistered to the pre-HSCT MR images, with visual confirmation to ensure that the same anatomic site of the LEE was measured across time. Relative values of each parameter were calculated from the POWM, SCC, or LEE by dividing by the value of that parameter with the measurement obtained from NAFWM; the exception was that only raw K2 was recorded because relative K2 cannot be calculated given its zero value within the NAFWM.

**MR Imaging Severity Scoring (Loes Score)**

Two neuroradiologists with ≥5 years’ experience with cALD (D.J.L, D.R.N.) reviewed the FLAIR images by consensus to generate MR imaging severity (Loes) scores. This review was performed according to the method of prior studies. Both neuroradiologists were blinded to the clinical data.

**Measurement of Clinical Outcome**

The gross neurologic function at baseline (pre-HSCT) and 1 year post-HSCT was determined by using a previously described 25-point cALD severity neurologic function scale; notably, increasing scores on the scale denote worsening function. For the cALD cohort, the neurologic function scale was retrospectively constructed from detailed clinical assessments in the medical record by a pediatric HSCT specialist (W.P.M.). Neurocognitive scores from the Wechsler Intelligence Scale Series, including full-scale intelligence quotient, performance intelligence quotient, and verbal intelligence quotient, were prospectively obtained by dedicated examination from 1 of several neuropsychologists both pre-HSCT and at 1 year, as described previously. Both the pediatric transplantation specialist

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**FIG 2.** Example of DSC-MRP measurements in a 10-year-old boy with cALD. Baseline (pre-HSCT) MR images show the LEE (arrows) on postcontrast TIWI (A), with typical findings of posterior-type cALD on FLAIR at that time (B). On DSC-MRP at that time, both rCBV (C) and rCBF (D) are mildly elevated at the LEE (arrows) but appear low centrally within the POWM (asterisks). G. The method of relative peak height measurement within the LEE and NAFWM ROIs on the baseline (pre-HSCT) MR imaging examination, via measurement of the dynamic contrast curve. Follow-up MR imaging at 1 year shows that the LEE has resolved on postcontrast TIWI (E) and that the WM abnormalities did not progress on FLAIR (F), though moderate overlying parieto-occipital-predominant atrophy has ensued, with interval sulcal enlargement.
and the neuropsychologists were blinded to the MR imaging data.

**Statistical Analysis**

Mann-Whitney tests were used to assess differences between patients with cALD and controls regarding the regional DSC-MRP values at each MR imaging time point (notably, the MRP values at a single time point in controls were compared for each of the 3 cALD cohort time points). Intrapatient pre- and post-HSCT MRP values were compared via the linear mixed model, with P value adjustment for multiple comparisons applied by using the Tukey method. Both the pre-HSCT (baseline) MRP values and the Loes scores were correlated with the 1-year clinical outcome functional and neurocognitive scores (neurologic function scale, full-scale intelligence quotient, performance intelligence quotient, and verbal intelligence quotient) by the Spearman method. Statistical analyses were performed by using SAS software (Version 9.3; SAS Institute, Cary, North Carolina). The significance threshold was set to P < .05.

**RESULTS**

Ten boys with cALD were ultimately included for analysis from the initial population of 47 males with ALD who were evaluated in the clinic during the same period. Reasons for exclusion are provided in Fig 1. Neither the baseline ages nor the Loes scores differed between the included and excluded patients (both P > .05).

The mean age at baseline MR imaging for the 10 patients was 8.2 ± 2.7 years (range, 5–14 years), and for controls, it was 7.8 ± 3.2 years (range, 4–12 years); these ages were not significantly different (P = .748). During the study period, none of the 10 patients with cALD incurred other cerebral pathology that confounded the DSC-MRP evaluation. The mean MRP measurements for the cALD cohort at all 3 time points are provided, with P values when comparing with controls, in Table 1.

Regarding the SCC, both rCBV and rCBF were significantly less in patients than in controls at both baseline and 1-year post-HSCT (Table 1). At the 30- to 60-day post-HSCT time point, only rPH significantly differed between patients and controls. As for intrapatient rCBV and rCBF, both parameters decreased from pre- to 1-year post-HSCT by 5.6% and 10.0%, respectively; however, such changes were not statistically significant between the 2 time points for either parameter (P = .057–.076).

As for the POWM, there were significant differences between the patients with cALD and controls; rCBV, rCBF, and rTTP differed significantly between patients and controls at all 3 time points (Table 1). Within the cALD cohort, both intrapatient rCBV and rCBF decreased from the pre- (baseline) to 1-year post-HSCT time points by 30.7% and 33.0%, respectively; however, these were not found to be significantly different between the 2 time points for either parameter (P = .101–.118).

All patients had an enhancing LEE before HSCT, and each had resolution of that visibly enhancing edge by 1 year post-HSCT (Figs 2–4). Within the LEE, the day 30–60 rPH was the only MRP parameter that differed significantly between the 10 patients with cALD and controls, while the pre- (baseline) and 1-year post-

**FIG 3.** A 6-year-old boy with cALD. Pre-HSCT, a LEE (arrows) is present along the anterior SCC on postcontrast TIWI (A), with edema on FLAIR within the SCC and, to a lesser degree, within the POWM (B). Also at baseline, the CBV (C) and CBF (D) maps demonstrate ROIs obtained from the NAFWM, POWM, and SCC. After HSCT, on 1-year follow-up postcontrast TIWI (E), the LEE has disappeared, with decreased swelling and no worsening of the extent on FLAIR (F). Note that the sagittal postcontrast TIWI at 1 year (G) demonstrates the disappearance of the enhancing LEE (arrow) within the SCC, compared with the initial postcontrast image at baseline (H).
HSCT values did not (Table 1). Regarding the LEE within the cALD cohort, the intrapatient rCBV and rCBF both decreased by 9.4% and 7.9%, respectively, though neither these nor any other measured MRP parameter changed significantly between the baseline and 1-year time points ($P > 0.142–0.887$).

Regarding the Loes MR imaging severity scores, the mean Loes scores at each time point for the cALD cohort (based on FLAIR) were $6.35 \pm 5.5$ at baseline (pre-HSCT), $6.40 \pm 5.5$ at 30–60 days post-HSCT, and $7.90 \pm 5.6$ on the 1-year follow-up MR imaging examinations. As would be expected on the basis of prior literature, the pre-HSCT Loes score strongly correlated with the 1-year clinical neurologic function scale score ($r = 0.813$, $P < .0001$).9,10,19 Regarding the neurocognitive measures, moderate correlations existed between the baseline Loes score and the 1-year neurocognitive full-scale intelligence quotient, performance intelligence quotient, and verbal intelligence quotient.

![FIG 4. A 15-year-old adolescent boy with ALD. Pre-HSCT postcontrast T1WI (A) demonstrates a LEE (arrows) in the POWM and optic radiations, with edema on noncontrast FLAIR (B). Baseline pre-HSCT ROIs from the NAFWM, POWM, and SCC are depicted on postcontrast T1WI (A) and on the MRP CBV (C), CBF (D), TTP (G), and K2 (H) maps. After HSCT, the 1-year follow-up MR imaging demonstrates resolution of the LEE on postcontrast T1WI (E), with no overt change in the extent of abnormality on FLAIR (F), though mild-moderate cerebral atrophy has ensued, being more prominent within the SCC.](image-url)

### Table 1: Mean of DSC-MRP parameters with $P$ values comparing patients with ALD with controls at each time*

<table>
<thead>
<tr>
<th>DSC-MRP Parameter</th>
<th>Pre-HSCT Mean</th>
<th>$P$ Value versus Controls</th>
<th>Post-HSCT (30–60 Days) Mean</th>
<th>$P$ Value versus Controls</th>
<th>Post-HSCT (1 year) Mean</th>
<th>$P$ Value versus Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC: rCBV</td>
<td>0.71 ± 0.32</td>
<td>.005&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.02 ± 0.47</td>
<td>.404</td>
<td>0.67 ± 0.25</td>
<td>.005&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCC: rCBF</td>
<td>0.70 ± 0.34</td>
<td>.005&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00 ± 0.47</td>
<td>.553</td>
<td>0.63 ± 0.24</td>
<td>.003&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCC: rTTP</td>
<td>0.26 ± 1.83</td>
<td>.813</td>
<td>0.13 ± 1.51</td>
<td>.887</td>
<td>0.35 ± 0.29</td>
<td>.377</td>
</tr>
<tr>
<td>SCC: rPH</td>
<td>0.96 ± 0.38</td>
<td>.093</td>
<td>0.85 ± 0.30</td>
<td>.025&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.82 ± 0.36</td>
<td>.019&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SCC: K2</td>
<td>0.004 ± 0.001</td>
<td>.177</td>
<td>0.00 ± 0.00</td>
<td>.824</td>
<td>0.00 ± 0.00</td>
<td>.999</td>
</tr>
<tr>
<td>POWM: rCBV</td>
<td>0.72 ± 0.30</td>
<td>.031&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.63 ± 0.31</td>
<td>.004&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.50 ± 0.40</td>
<td>.004&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>POWM: rCBF</td>
<td>0.70 ± 0.27</td>
<td>.023&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.61 ± 0.30</td>
<td>.004&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.47 ± 0.34</td>
<td>.004&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>POWM: rTTP</td>
<td>1.92 ± 1.46</td>
<td>.007&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.95 ± 0.95</td>
<td>&lt;.00&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.42 ± 5.22</td>
<td>.043&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>POWM: rPH</td>
<td>1.19 ± 0.26</td>
<td>.092</td>
<td>0.92 ± 0.34</td>
<td>.552</td>
<td>0.87 ± 0.38</td>
<td>.238</td>
</tr>
<tr>
<td>POWM: K2</td>
<td>0.002 ± 0.003</td>
<td>.662</td>
<td>0.00 ± 0.00</td>
<td>.999</td>
<td>0.00 ± 0.00</td>
<td>.999</td>
</tr>
<tr>
<td>LEE: rCBV</td>
<td>1.38 ± 0.63</td>
<td>.168</td>
<td>1.43 ± 0.62</td>
<td>.301</td>
<td>1.25 ± 0.48</td>
<td>.618</td>
</tr>
<tr>
<td>LEE: rCBF</td>
<td>1.39 ± 0.64</td>
<td>.153</td>
<td>1.43 ± 0.66</td>
<td>.651</td>
<td>1.28 ± 0.46</td>
<td>.554</td>
</tr>
<tr>
<td>LEE: rTTP</td>
<td>0.24 ± 1.34</td>
<td>.982</td>
<td>−0.11 ± 0.88</td>
<td>.432</td>
<td>−1.29 ± 3.76</td>
<td>.601</td>
</tr>
<tr>
<td>LEE: rPH</td>
<td>1.62 ± 0.67</td>
<td>.074</td>
<td>1.43 ± 0.43</td>
<td>.020&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.12 ± 0.46</td>
<td>.459</td>
</tr>
<tr>
<td>LEE: K2</td>
<td>0.004 ± 0.005</td>
<td>.177</td>
<td>0.00 ± 0.00</td>
<td>.662</td>
<td>0.00 ± 0.003</td>
<td>.999</td>
</tr>
</tbody>
</table>

* The relative MRP ratios in patients with ALD compared with NAFWM.

<sup>b</sup>$P$ values < .05.
scores, but these did not reach clinical significance \((r = -0.596 \text{ to } -0.646, P = 0.068 \text{ to } 0.90)\) after correction for multiple comparisons (Table 2).

Regarding correlating the baseline DSC-MRP parameters with the functional and neurocognitive scores at 1 year post-HSCT, the only parameters that correlated with the clinical and neurocognitive outcomes were rCBV and rCBF within the SCC (Table 2). In particular, baseline SCC rCBV had an inverse, significant correlation with the clinical neurologic function scale score at 1 year \((r = -0.730, P = 0.016)\) and a positive correlation with the neurocognitive scores full-scale intelligence quotient \((r = 0.735, P = 0.038)\) and performance intelligence quotient \((r = 0.843, P = 0.045)\). Notably, no significant correlation was found between any regional MRP parameter and the 1-year neurocognitive verbal intelligence quotient scores, after correction for multiple comparisons. Additionally, no MRP measure within the POWM or LEE significantly correlated with the 1-year neurologic function scale or neurocognitive outcome scores (each \(P > 0.05\)).

**DISCUSSION**

Because childhood cALD is typically a progressive and severe disorder in the absence of HSCT, the primary goals of this study were the following: 1) to determine whether MRP parameters differ from those in controls in various regions of the cALD-affected brain, 2) to describe a variety of DSC-MRP parameters both pre- and post-HSCT, and 3) to determine whether any baseline (pre-HSCT) MRP markers portend the clinical outcome following HSCT.6-12 Regarding the former goal, both this study and that of Musolino et al12 found that rCBV was preserved within the LEE that persists after HSCT. Meanwhile, the arrest of enhancement at the LEE, along with the preserved rCBV and rCBF at 1 year post-HSCT, would imply viable tissue therein. Notably, in our cohort, the POWM rCBV was, on average, about 50% of that of the NAFWM, whereas the rCBV was about 20% of that of the NAFWM in the prior study.12 This difference in rCBV could relate to the higher mean Loes score (13.4 versus 6.4 in this study) in the prior study, perhaps reflecting more severe tissue injury overall.12

The mechanism of how HSCT attenuates the neuroinflammation in cALD is unknown; however, the normal rCBV within the LEE that persists after HSCT suggests a correction of the blood-brain barrier abnormality, along with preservation of regional parenchyma.13-15,10-12 Similarly, the study by Musolino et al11 found that rCBV was preserved in the LEE (termed “Zone B”) but was lower in adjacent, centrifugally located areas (Zone C); hence, the current study corroborates the Zone B findings of that study. Such an arrest in demyelination may have a histopathologic precedent, in which murine studies have shown that certain microglial cells are absent initially at the demyelinating edge, but there is a subsequent slow return of microglial guard cells by about 1 year post-HSCT as progression of the disease halts.22-26 Thus, 1 theory, which remains speculative, is that blood-brain barrier dysfunction is actually helpful or is required for the marrow-derived precursor cells to return into the cerebrum and differentiate into microglia because a LEE is nearly always present before HSCT in those patients who have undergone a successful HSCT and ultimately have stabilized cerebral disease.22-26 Thus, this theory suggests that microglia reflect an overall return of hematopoietic precursor stem cells to the cerebrum, resulting in the observed disease arrest, along with the subsequent repair.22-26 Zonal measurements within and adjacent to the LEE were not the focus of the current study but could be considered in future ones.

Regarding the SCC, this aforementioned theory may, at least in part, explain the lack of a significant difference in the large majority of the various MRP measures at 30–60 days post-HSCT, even though there were significant differences at baseline and at 1 year post-HSCT (especially in rCBV and rCBF).22-26 Thus, we surmise that there could be both components of irreversible injury and healing of the blood-brain barrier occurring macroscopically in the SCC, which may be an “inflection point” in the disease process. For example, according to the above-mentioned theory, HSCT can correct the underlying microglial dysfunction by way of bone marrow resident and progenitor cells entering the cerebrum through a patent and abnormal blood-brain barrier via capillary recruitment and resultant increased microperfusion; we opine that this might be represented by a transient relatively decreased rTTP and relatively increased rCBV and CBF.22-26 In the current study, such transient changes (ie, increased rCBF and rCBV) were indeed noted in the SCC, where the rTTP transiently

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**Table 2: Correlations between both the pre-HSCT MRI severity and MRP parameters with the 1-year follow-up clinical outcome scores**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NFS</th>
<th>FSIQ</th>
<th>PIQ</th>
<th>VIQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC: rCBV</td>
<td>-0.730, .016&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.735, .038&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.815, .007&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.500, .171</td>
</tr>
<tr>
<td>SCC: rCBF</td>
<td>-0.451, .191</td>
<td>0.590, .123</td>
<td>0.678, .045&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.233, .546</td>
</tr>
<tr>
<td>SCC: rTTP</td>
<td>-0.291, .414</td>
<td>0.205, .627</td>
<td>0.033, .932</td>
<td>0.400, .286</td>
</tr>
<tr>
<td>SCC: rPH</td>
<td>0.181, .745</td>
<td>-0.012, .977</td>
<td>0.059, .881</td>
<td>-0.017, .966</td>
</tr>
<tr>
<td>POWM: rCBV</td>
<td>-0.555, .096</td>
<td>0.325, .432</td>
<td>0.301, .431</td>
<td>0.367, .332</td>
</tr>
<tr>
<td>POWM: rCBF</td>
<td>-0.557, .095</td>
<td>0.325, .432</td>
<td>0.301, .431</td>
<td>0.360, .342</td>
</tr>
<tr>
<td>POWM: rTTP</td>
<td>0.569, .086</td>
<td>-0.663, .073</td>
<td>-0.619, .075</td>
<td>-0.550, .125</td>
</tr>
<tr>
<td>POWM: rPH</td>
<td>0.326, .358</td>
<td>-0.036, .932</td>
<td>-0.126, .748</td>
<td>0.250, .517</td>
</tr>
<tr>
<td>LEE: rCBV</td>
<td>0.045, .901</td>
<td>-0.217, .606</td>
<td>-0.126, .748</td>
<td>-0.326, .391</td>
</tr>
<tr>
<td>LEE: rCBF</td>
<td>-0.090, .804</td>
<td>0.024, .955</td>
<td>0.042, .915</td>
<td>-0.017, .967</td>
</tr>
<tr>
<td>LEE: rTTP</td>
<td>0.083, .819</td>
<td>-0.217, .606</td>
<td>-0.226, .559</td>
<td>-0.150, .700</td>
</tr>
<tr>
<td>LEE: rPH</td>
<td>0.111, .760</td>
<td>-0.506, .201</td>
<td>-0.452, .222</td>
<td>-0.250, .517</td>
</tr>
<tr>
<td>Loes score</td>
<td>0.813, &lt;.0001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.646, .084</td>
<td>-0.633, .068</td>
<td>-0.596, .090</td>
</tr>
</tbody>
</table>

**Note:** NFS indicates neurologic function scale; FSIQ, full-scale intelligence quotient; PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient.

<sup>b</sup> Numbers are rounded to the one-thousandth place. In addition, the correlations for K2 are not shown because most measurements were 0.00.

<sup>12</sup> \(P \) values < .05.
decreased at 30–60 days post-HSCT and then rose again to above baseline at 1 year post-HSCT. However, by 1 year post-HSCT, both SCC rCBF and rCBV decreased to below baseline, suggesting that such increased perfusion at 30–60 days post-HSCT was indeed only a temporary phenomenon.

Hence, the measurements at 30–60 days post-HSCT might reflect an attempt for the cerebrum to undergo healing by temporarily increasing perfusion to the SCC by a vascular response, though there is also likely a component of underlying irreversible injury, as evidenced by the lower 1-year rCBV and rCBF values. If so, then this combination of findings might explain the SCC being the 1 site where the baseline DSC-MRP measurements predict the neurocognitive outcomes (hence, the term “inflection point”) because it is a region that has both viable tissue that can potentially be saved, along with nonviable tissue. In contrast, the POWM appears to be a region where the tissue injury is largely irreversible, as evidenced by the lack of such transient findings at 30–60 days post-HSCT. Accordingly, within the POWM, rTTP remained higher and rCBV and rCBF both progressively decreased after HSCT. Thus, the POWM seems mostly unaffected by successful transplantation.

This study also found that the baseline SCC rCBV and rCBF values strongly correlated with various measures of neurologic function at 1 year after successful HSCT, perhaps due to the reasons described above. While the Loes MR imaging score is known to correlate with the gross neurologic outcome after HSCT, the findings in the current study suggest that regional DSC-MRP values could augment the Loes score in predicting outcomes better.7-11 However, this study was limited, in that most boys within the cohort had generally favorable baseline Loes scores. Hence, these findings may not be applicable to those patients with more severe initial disease. Thus, the utility of MRP in predicting outcomes in patients with cALD with more severe disease needs to be further studied.

There has been an ongoing search for the best baseline (pre-HSCT) imaging marker of clinical outcome following transplantation (HSCT). Regarding such biomarkers, to our knowledge, the Loes score is the most reproducible and strongest predictor of outcome, being proved across multiple centers.6-10 While the Loes score is a “continuous” marker of radiographic severity being the 1 site where the baseline DSC-MRP values predict the neurocognitive outcomes (hence, the term “inflection point”) because it is a region that has both viable tissue that can potentially be saved, along with nonviable tissue. In contrast, the POWM appears to be a region where the tissue injury is largely irreversible, as evidenced by the lack of such transient findings at 30–60 days post-HSCT. Accordingly, within the POWM, rTTP remained higher and rCBV and rCBF both progressively decreased after HSCT. Thus, the POWM seems mostly unaffected by successful transplantation.

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CONCLUSIONS

This study found that certain DSC-MRP values in patients with cALD, as measured within the POWM and SCC pre-HSCT, are significantly different from those in controls, while the LEE values are not. With time, rCBV within the LEE remained normal in the patients with cALD relative to controls. This outcome suggests stabilization of a dysfunctional blood-brain barrier at the LEE; conversely, the finding that rCBV worsens within the POWM following HSCT suggests irreversible injury. This study also found that the rCBV is the only baseline MRP measurement that
seems to be a reliable predictor of clinical outcome. Thus, MRP could be a useful adjunct to the Loes MR imaging severity score in predicting the functional and neurocognitive outcomes of boys with cALD who are to undergo HSCT.


REFERENCES