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Original Article

Diffusion Imaging of Cerebral Diaschisis in Neonatal Arterial Ischemic Stroke

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ABSTRACT

Background: Neonatal arterial ischemic stroke is a leading cause of cerebral palsy and lifelong disability. Diffusion-weighted imaging has revolutionized diagnosis and facilitated outcome prognostication in acute neonatal arterial ischemic stroke. Diaschisis refers to changes in brain areas functionally connected but structurally remote from primary injury. We hypothesized that acute diffusion-weighted imaging can quantify cerebral diaschisis and is associated with outcome from neonatal arterial ischemic stroke.
Methods: Subjects were identified from a prospective, population-based research cohort (Alberta Perinatal Stroke Project). Inclusion criteria were unilateral middle cerebral artery neonatal arterial ischemic stroke, diffusion-weighted magnetic resonance imaging within 10 days of birth, and more than 12-months follow-up (pediatric stroke outcome measure). Diaschisis was characterized and quantified using a validated software method (*ImageJ*). Volumetric analysis assessed atrophy of affected structures. Diaschisis scores were corrected for infarct size and compared with outcomes (Mann-Whitney).
Results: From 20 eligible neonatal arterial ischemic strokes, two were excluded for poor image quality. Of 18 remaining (61% male, median age 3.2 days), 16 (89%) demonstrated diaschisis. Thalamus (88%) was the most common location in addition to corpus callosum (50%). Age at imaging was not associated with diaschisis. Affected structures demonstrated atrophy on imaging. Long-term outcomes available in 81% (median age 7.5 years) were not associated with diaschisis scores.
Conclusions: Cerebral diaschisis occurs in neonatal arterial ischemic stroke and can be quantified with diffusion-weighted imaging. Occurrence is common and should not be mistaken for additional infarction. Determining clinical significance will require larger samples with well-characterized long-term outcomes.

Introduction

Acute symptomatic neonatal arterial ischemic stroke (NAIS) is a leading cause of early brain injury, hemiparetic cerebral palsy, and lifelong disability. Most children with NAIS incur neurological morbidity including sensorimotor deficits, cognitive and behavioral disorders, and epilepsy.[1]

Accurate early prediction of outcome after NAIS is difficult and has been increasingly facilitated by magnetic resonance imaging (MRI). Lesion size and location have only modest associations with long-term outcome.[2-4] Diffusion-weighted imaging (DWI) may offer additional predictive utility. The presence and extent of DWI restriction in the ipsilateral descending corticospinal tracts have been specifically associated with poor motor outcome (hemiplegic cerebral palsy) in NAIS[5,6] as well as childhood[7] and adult[8] stroke. More advanced diffusion imaging can further inform early

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prognostication.[9] Such improved ability to predict the most common morbidity of NAIS has improved counseling of families and selection of patients for emerging acute neuroprotection trials.

However, there remain virtually no means by which the non-motor outcomes of NAIS can be predicted in the acute setting. Diffusion MRI may be able to demonstrate early degenerative changes in other brain areas remote from the stroke. A small study described such changes in the pulvinar region of the thalamus after neonatal brain injury to more distal pathways.[10] Such secondary changes in brain areas remote from, but connected to, stroke lesions may represent diaschisis.

Neuropathologist Constantin von Monakow introduced the term diaschisis in 1902 to differentiate between the focal consequences of direct neural injury from more distant effects in the brain.[11] Cerebral diaschisis may be considered as alterations in brain areas that are functionally connected but structurally remote from the primary site of brain injury. The process of crossed cerebellar diaschisis is well described in adult stroke[12,13] and demonstrated in children with stroke where acute diffusion changes of cortico-ponto-cerebellar pathways were predictive of chronic atrophy.[14] We have demonstrated that DWI indications of extensive diaschisis are common in childhood arterial ischemic stroke and may relate to outcome.[15] We also recently found that crossed cerebellar diaschisis occurs in NAIS.[16] Acute cerebral diaschisis in NAIS and its association with outcome has not been defined.

We conducted a retrospective observational study to characterize cerebral diaschisis in NAIS and its potential relationship with neurological outcome. We hypothesized that larger extents of acute diaschisis would be related to poorer motor outcomes.

Materials and methods

Study population

This was a retrospective observational study with data collected from a population-based research cohort (Alberta Perinatal Stroke Project[17]). Criteria for inclusion consisted of term birth (greater than 36 weeks' gestation), MRI-confirmed unilateral middle cerebral artery arterial ischemic stroke (AIS), availability of diffusion-weighted MRI within 10 days of birth, follow-up at age 12 months or later with the pediatric stroke outcome measure (PSOM), and informed consent. Participants with additional brain injury or other neurological disease were excluded.

Neuroimaging analyses

Original, clinically obtained MRIs were securely transferred to the Alberta Children's Hospital Pediatric Neuroimaging Laboratory for analysis. Axial diffusion images ($b = 1000$) were analyzed using a validated *ImageJ* Software protocol.[18] Briefly, the presence of single, acute AIS in the middle cerebral artery territory was confirmed and areas of potential diaschisis were then visually sought. The following criteria were required to define abnormal diffusion signal as diaschisis: (1) anatomic connection of affected structure to the area of stroke, (2) arterial territory independent from that of the primary stroke, and (3) restricted diffusion seen as hyperintensity on DWI with corresponding hypointensity on apparent diffusion coefficient maps of equal or lesser intensity to that of the primary infarct.

Methods of identifying and calculating diaschisis have been previously described in detail for childhood AIS[15] and were replicated for this study. Once definitive diaschisis was visually assessed, the following imaging outcomes were determined:

- *Diaschisis*. All anatomic locations demonstrating diaschisis were recorded. The most representative slice of diaschisis was selected, with the corresponding area(s) of the nonlesioned hemisphere considered normal. The upper and lower limits of the ImageJ threshold tool (0° to 256°) were then adjusted upward until a single pixel became positive in the nonlesioned hemisphere location corresponding to the area of maximal diaschisis in the lesioned hemisphere. The value was then reduced by one to set the threshold for diaschisis signal. This area was captured and recorded using the measurement tool. These same threshold parameters were then applied to all remaining slices. All area measurements captured were summated through sequential slices to produce a total diaschisis volume.
- *Perilesional diaschisis*. To quantify diaschisis immediately surrounding the primary infarct, the upper limit was set by adjusting the threshold to exclude the infarct core, as defined by the most hyperintense areas of restricted diffusion.
- *Stroke volume*. The threshold tool of ImageJ was adjusted upward until the first positive pixel was detected in the nonlesioned hemisphere. The threshold was then adjusted down one with all remaining positive pixels considered abnormally hyperintense. The measurement tool was then applied to capture the area of hyperintensity on that slice. This process was repeated across all slices containing infarct with the values summated to create total infarct volume.
- *Whole brain volume*. The same aforementioned threshold method was applied to all slices to highlight all brain parenchymal signal. These areas were summed to generate whole brain volume.
- *Diaschisis score (D score)*. A diaschisis score that corrected for infarct size was calculated as follows: D score = [diaschisis volume/(infarct volume/whole brain volume)]. This D score was the primary imaging outcome variable.

Scans were originally scored by a single investigator who was not aware of all clinical data including neurological outcomes. A subset of six scans was randomly selected and rescored by the same investigator more than two weeks later to assess intrarater reliability. Another subset of six scans was randomly selected and analyzed by a separate team member who was not aware of both outcomes and the previous scoring to assess inter-rater reliability.

Clinical outcomes

Neurological outcome was quantified using the PSOM. The PSOM is a validated, disease-specific, standardized outcome measure for the long-term effects of stroke in children.[19] Neurological deficits are measured by clinical evaluation and examination across five subscales: right sensorimotor, left sensorimotor, language production, language comprehension, and cognitive and behavior. Summary scores are 0 (no deficit), 0.5 (mild with no functional impact), 1 (moderate), or 2 (severe). Consistent with the previously published literature using PSOM, motor and overall PSOM scores were dichotomized as good (0 to 0.5) versus poor (1 to 2).

Statistical analyses

Descriptive analyses of the population and diaschisis imaging characteristics were performed. Distribution normality was assessed using Shapiro-Wilk tests. Mann-Whitney's U test was used to compare continuous variables (D scores) between outcome groups and Levene's test for equality of variance explored differences in variance. Spearman's rho explored relationships between total diaschisis, D scores, infarct core volumes, and motor outcomes.

Intraclass correlation coefficients (ICCs) were used to assess method reliability. Analyses were performed using SPSS version 13.

Results

Twenty participants met initial inclusion criteria. Two were excluded because of poor scan quality. The final study population consisted of 18 children (39% female), the characteristics of which are summarized in Table. Median age at MRI was 72 hours (S.D. = 34, range 7.9 to 131 hours).

ICCs revealed excellent intrarater (ICC = 0.87) and inter-rater (ICC = 0.96) reliability for the diaschisis quantification technique. Of the 18 participants, 16 (89%) had at least one area of diaschisis identified (10 males, six females). Representative examples are presented in Fig 1. Most (14/16, 88%) had more than one area of diaschisis. The thalamus (87.5%) and corpus callosum (50%) were the most common locations where diaschisis was observed. Total volume of diaschisis was correlated with infarct core volume ($\rho = 0.715$, $P = 0.002$; Fig 2).

All participants had available follow-up assessments at age 12 months or later (median 88 months, range 12 to 142). For overall PSOM, 88% of participants had good outcome (no functional deficits), which was predominantly affected by the cognitive and behavior score as 100% of participants had positive scores on this subtest. When looking specifically at the motor component of the PSOM, 69% were categorized as good with 31% as poor (moderate to severe deficits).

Median *D* scores were not significantly different between those with good and poor PSOM motor outcomes ($P = 0.180$; Fig 3); however, those with poor PSOM had significantly higher variability in *D* scores [poor PSOM (1 to 2) median *D* score = 700.8 (interquartile region 1460.5) versus good PSOM (0 to 0.5) median *D* score = 399.2 (interquartile region 684.4); $P = 0.02$]. The amount of diaschisis as estimated by the *D* score was not significantly associated with age at MRI. Motor function was not significantly associated with total infarct size ($\rho = 0.64$, $P = 0.12$) or *D* score (when corrected for infarct volume $\rho = 0.39$, $P = 0.15$).

Discussion

Our study provides novel evidence that DWI can identify early changes in brain structures remotely connected to areas of primary injury in NAIS. The most common locations for such diaschisis were highly connected structures in different arterial territories including the thalamus and corpus callosum. Our modest sample, simple outcome measures, and short follow-up period were unable to fully explore potential associations with long-term neurological outcome.

The concept of diaschisis is not new. Overt neuropathologic descriptions were made over 100 years ago, validating the concept of remote effects in brain structures connected to, but discrete from, a primary area of injury.[11] Although diffusion imaging might only be considered a proxy of such histologic processes, our findings here of specific and acute changes in structures connected to, but within different arterial territories from, the original stroke are consistent with the diaschisis concept. These findings have been identified in children[15] but have only rarely been described in neonates. Govaert et al.[10] described remote diffusion changes in the pulvinar nucleus in seven newborns with arterial ischemic stroke and suggested that they might represent signs of "network injury," a concept we would agree with and one supported by the results of the present study.

Age appears to be associated with DWI markers of diaschisis. Despite the much higher incidence of stroke in adults, the concept of diaschisis has not been well explored in this population. A relevant analogy is the description of pre-Wallerian degeneration in the corticospinal tracts, which was also first described in neonates,[6,20] then in children,[7] and eventually extrapolated to adults with stroke.[8] A study of childhood stroke diaschisis[15] also found an inverse association between age at stroke and the presence of diaschisis. Theories to explain why younger brains may be better able to demonstrate diaschisis on DWI include developmental differences in myelination, brain water content, or differential effects on structural or functional connectivity.[15] Another possible factor is that both acute and serial MRI scans are less often performed in adults with stroke whereas they are the standard for

TABLE.
Patient Characteristics, Diaschisis, and Outcomes

Patient	Sex	Age at MRI (hours)	Cerebral Diaschisis	Diaschisis Location	PSOM		
					Motor	Nonmotor	Overall
1	M	103	Yes	Thalamus, CC, peduncle	Poor	Good	Poor
2	F	142	Yes	Caudate, thalamus, CC, peduncle	Poor	Good	Good
3	F	103	Yes	Thalamus, CC, peduncle	Good	Good	Good
4	F	98	Yes	Thalamus, CC, peduncle	Good	Good	Good
5	F	112	Yes	Thalamus	Poor	Good	Good
6	M	67	Yes	Thalamus	Good	Good	Good
7	F	91	Yes	Caudate, thalamus	Good	Good	Good
8	M	105	Yes	Caudate, thalamus, CC, peduncle	Poor	Poor	Poor
9	M	66	Yes	Thalamus, peduncle	Good	Good	Good
10	M	88	Yes	Thalamus, peduncle	Poor	Good	Good
11	M	60	Yes	Thalamus, CC	Good	Good	Good
12	M	21	Yes	Thalamus	Good	Good	Good
13	F	14	Yes	Putamen, CC	Good	Good	Good
14	M	13	Yes	Thalamus	Good	Good	Good
15	M	13	Yes	Internal capsule	Good	Good	Good
16	M	93	Yes	Thalamus, CC	Good	Good	Good
17	M	12	No	N/A	Good	Good	Good
18	F	6	No	N/A	Good	Good	Good

Abbreviations:
CC = corpus callosum
F = female
M = male
MRI = magnetic resonance imaging
PSOM = pediatric stroke outcome measure
PSOM scores were dichotomized into "good" (0 to 0.5, no deficit or no functional deficit) versus "poor" (1 to 2, moderate-severe deficit).

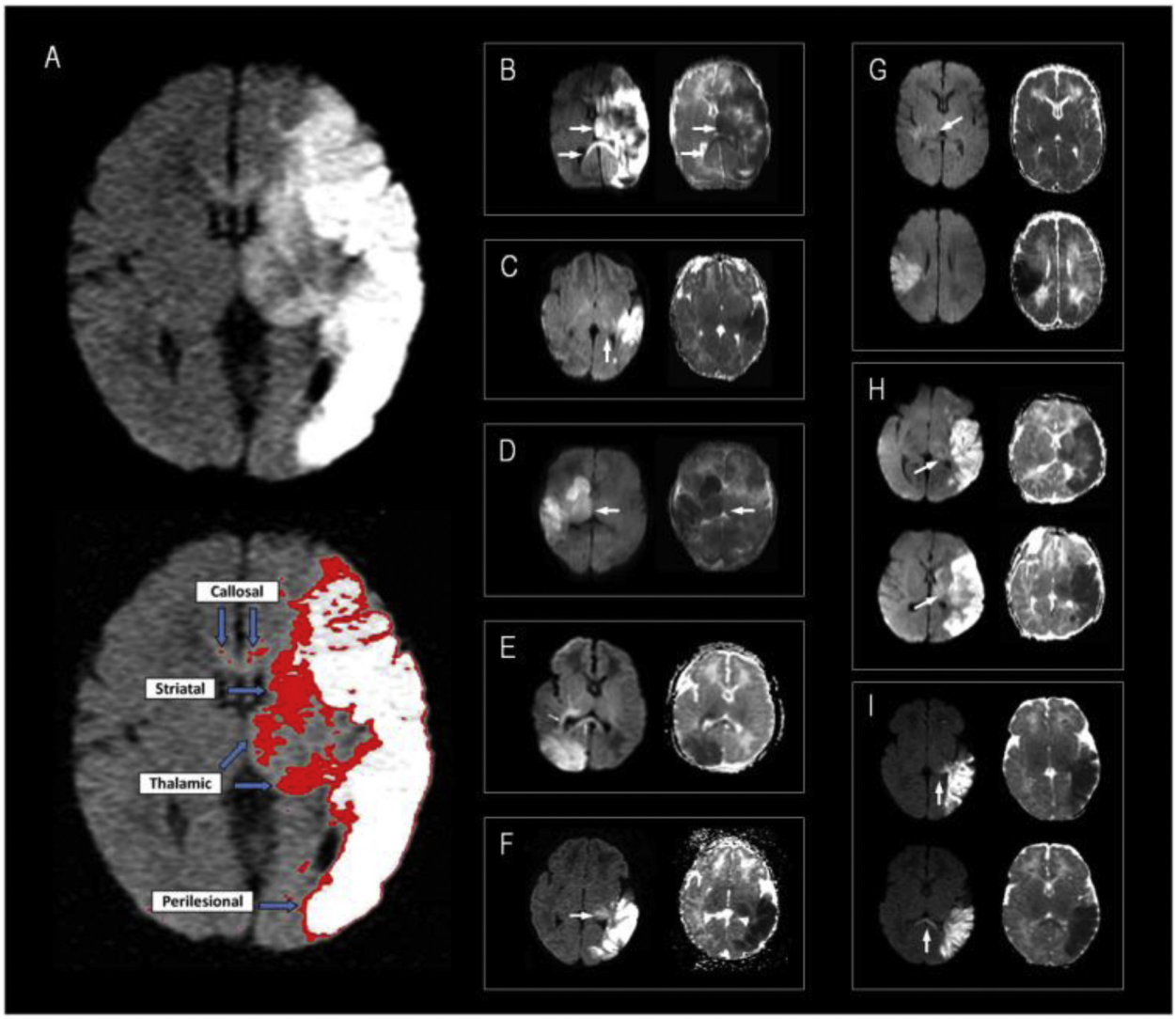

FIGURE 1. Diffusion imaging of cerebral diaschisis. (A) Axial slice of a distal middle cerebral artery occlusion neonatal arterial ischemic stroke shows restricted diffusion in the cortex but areas of lesser diffusion restriction in connected structures including the striatum, corpus callosum, and specific nuclei within the thalamus (top), The ImageJ thresholding method differentiates these areas and perilesional diaschisis (red) from the primary infarct (white, bottom). Panels B-I show individual examples of the same process. The color version of this figure is available in the online edition.

neonates, possibly increasing the likelihood of detecting diaschisis. Adult MRI scans may also be "contaminated" by small vessel white matter changes, potentially obscuring the ability to detect more subtle diffusion changes. Although the literature is scarce, it has been suggested that cerebral diaschisis may play a role in post-stroke recovery in hemiparetic adults,[21] possibly through neuronal reorganization after injury.[22] Further exploration of our findings in larger adult stroke populations may be able to shed more light on both mechanisms and clinical significance.

The thalamus and corpus callosum were the most common structures in which diaschisis was observed. Findings noted previously and in another study by Dudink et al.[23] supporting the concept of acute network injury in NAIS also demonstrated changes in the ipsilesional thalamus after primary stroke to connected cortical areas. A predilection for the thalamus is further supported by our descriptions of diaschisis patterns in childhood AIS.[15] Another recent study exploring chronic volumetric changes in remote structures after NAIS found both decreased ipsilesional and enlarged contralesional thalamic volumes, the degree of which correlated with clinical function.[24] This finding is not surprising if in fact these diffusion biomarkers reflect changes in connected structures where the thalamus is composed of densely packed gray matter with high connectivity to many cortical and subcortical structures commonly injured in NAIS. A similar rationale may explain the common occurrence of callosal diaschisis we observed where widespread connectivity to injured areas combined with densely packed and relatively unidirectional myelinated pathways might readily demonstrate changes in diffusion.

The relationship between diaschisis and outcome in NAIS remains to be determined. Although a possible association was suggested between poor motor outcome and the degree of diaschisis, this result did not reach statistical significance. Variability in the amount of diaschisis was significantly higher for the poor motor outcome group, further limiting the ability of our sample to detect associations with outcome but highlights the finding that some children with poor PSOM outcomes had similar diaschisis scores to those with good outcomes. Conversely, many children with poor PSOM motor outcomes had higher diaschisis scores. Although Levene's test is not optimized for use on such small sample sizes, it was used to statistically test the visual outcomes shown in Fig 3.

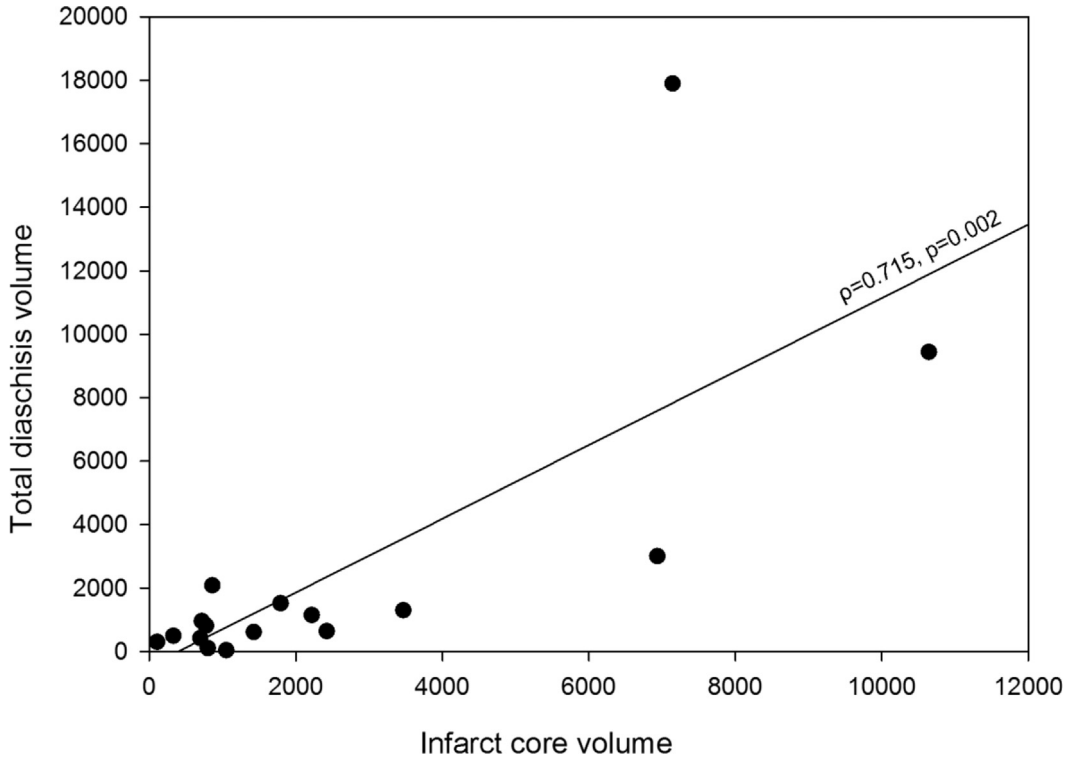

FIGURE 2. Relationship between cerebral diaschisis volume and infarct core volume. The relationship between total diaschisis and infarct core volumes (expressed as number of image voxels) is shown. Larger stroke was associated with greater diaschisis ($\rho = 0.715$, $P = 0.002$).

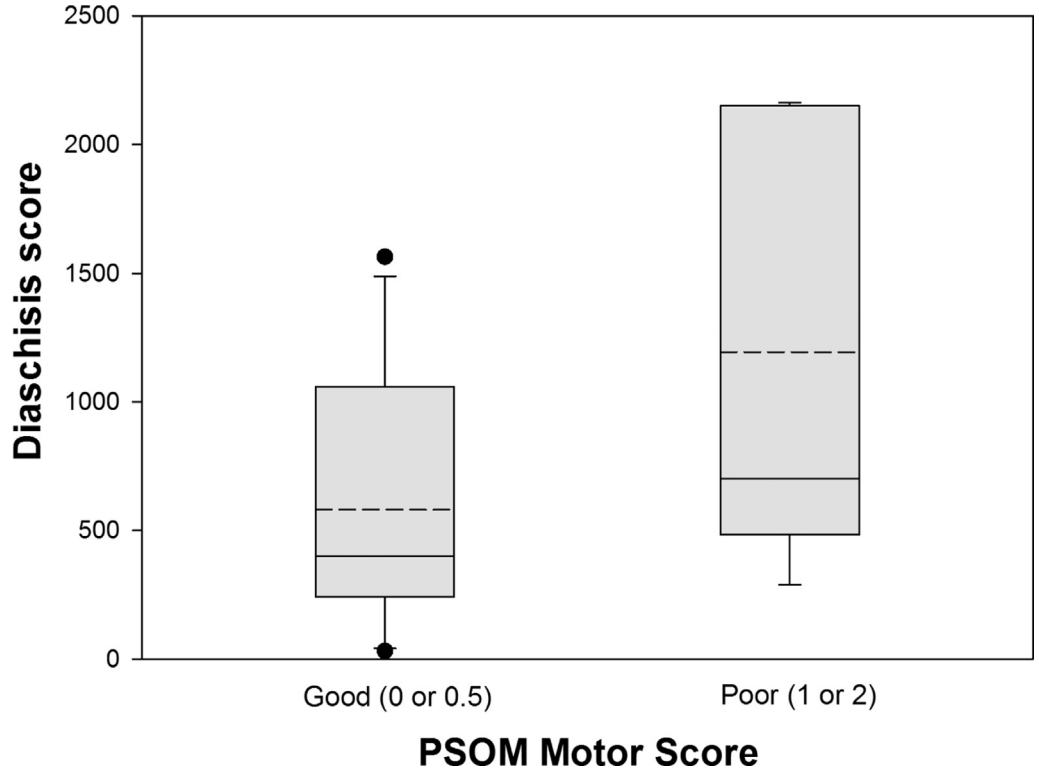

FIGURE 3. Relationship between motor outcome and amount of diaschisis. Box plots illustrating mean (dotted line), median (solid line), upper and lower quartiles, and outliers (black symbols) for diaschisis scores grouped by PSOM motor scores (good versus poor) are shown. Although the general trend appeared to show an association between poor motor outcome and amount of diaschisis, this finding was not statistically significant ($P = 0.180$). Those with poor PSOM scores showed significantly larger variance ($P = 0.02$) in diaschisis score. PSOM, pediatric stroke outcome measure.

A relationship between diaschisis and nonmotor cognitive impairments has been suggested in childhood ischemic stroke.[15] Motor skills tend to be more clinically apparent and relevant to families in the early stages of a child's development, and thus were the focus of our study in neonates. Our ability to explore nonmotor outcomes such as cognition and learning are limited by the same restrictions of all neonatal brain injury studies; the time required for children to grow into their deficits, a period of at least five to 10 years before neurodevelopmental outcomes can accurately be estimated. An interesting future direction will be to study the relationship between diaschisis and long-term cognitive outcomes in larger NAIS cohorts.

Our results may be clinically relevant in several regards. For one, improved clinical recognition of such diffusion markers of structurally remote but functionally connected changes is imperative in avoiding potential misdiagnoses of new or evolving injury. In our experience, restricted diffusion in the thalamus, brainstem, or corpus callosum has been mistakenly reported as evidence of additional infraction or perhaps a different mechanism of injury. This finding in turn might lead to unnecessary reimaging, further investigations, or parental angst. Potential translational significance might also be realized in improving the early prognostication of outcome in NAIS, which is not only of great value to parents but also to assist in patient selection for emerging neuroprotection clinical trials.[25] Finally, measuring diaschisis processes might further inform the models of developmental plasticity that are now guiding novel therapeutic trails for hemiparesis and other long-term deficits in perinatal stroke.[15] Although our study aimed to examine occurrence of diaschisis in a cross-sectional cohort of NAIS patients, future studies could attempt to quantify diaschisis over time with comparison between the atrophy seen on acute and chronic (follow-up) neuroimaging.

We acknowledge important limitations. Our sample size is modest, with limited power to detect primary associations. Our images were obtained on a clinical scanner going back a number of years, whereas modern technologies would likely afford better image quality and greater ability to detect and quantify diaschisis. There is also no gold standard for diagnosing diaschisis, and our results are potentially vulnerable to the bias of the investigators. Analysis was performed without knowing the results and used objective criteria, but improved methodologies, including the development of more automated imaging software pipelines, could further enhance the quality of metrics in this area. In addition, we did not establish the presence of structural connectivity between the area of diaschisis with the primary lesion using secondary techniques such as diffusion tensor imaging tractography or magnetic resonance spectroscopy. Rather, we assumed structural (and possibly functional) connectivity was implied by the presence of diaschisis. Future studies could directly quantify this connectivity using diffusion tensor imaging and relate this to both diaschisis volumes and function.

Conclusions

Our results support the ability of diffusion MRI to demonstrate acute processes consistent with cerebral diaschisis in NAIS. The occurrence of diaschisis is common, particularly in the thalamus and corpus callosum, and should not be mistaken for new or additional infarction. Determining additional clinical and prognostic significance will depend on larger samples with long-term outcomes. Longitudinal data from repeat MRI would contribute to the quantification of diaschisis and assessment of chronic atrophy.

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