Quantitative Sodium ($^{23}\text{Na}$) MRI in Pediatric Gliomas: Initial Experience

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Abstract

**Introduction:** The treatment of pediatric gliomas is typically assessed with proton (\(^1\)H) MRI, which can have limitations. \(^23\)Na MRI has been shown in adult brain tumors to measure intra-tumoral total sodium concentration as a correlate of tumor proliferation. \(^23\)Na MRI sodium studies in pediatric patients are lacking. The purpose of the study included: (1) To compare total sodium concentration (TSC) between pediatric glioma and non-neoplastic brain tissue using \(^23\)Na MRI; (2) Compare tissue conspicuity of bound sodium concentration (BSC) using \(^23\)Na MRI dual echo relative to TSC imaging.

**Methods:** TSC was measured in: (1) non-neoplastic brain tissues and (2) three types of manually segmented gliomas [diffuse intrinsic brainstem glioma (DIPG), recurrent supratentorial low-grade glioma (LGG), and high-grade glioma (HGG)] on sodium MRI images co-registered with proton MRI. In a subset of patients, serial changes in both TSC and BSC (dual echo \(^23\)Na MRI) were assessed for tissue conspicuity using voxel-based parametric maps.

**Results:** Twenty-six pediatric patients with gliomas (median age of 12.0 years, range 4.9 – 23.3 years) were scanned with \(^23\)Na MRI. Uninvolved tissues demonstrated a range of TSC values similar to published adult values. DIPG treated with RT demonstrated higher TSC values than the uninvolved infratentorial tissues (\(P<0.001\)). Recurrent supratentorial LGG and HGG exhibited higher TSC values than the uninvolved white matter (WM) and gray matter (GM) (\(P<0.002\) for LGG, and \(P<0.02\) for HGG). The dual echo \(^23\)Na MRI suppresses the sodium signal within both CSF and necrotic foci, resulting in improved conspicuity of both non-neoplastic and neoplastic, compared to serial TSC imaging.

**Conclusion:** Quantitative \(^23\)Na MRI of pediatric gliomas demonstrates a range of values that are higher than non-neoplastic tissues. Dual echo \(^23\)Na MRI of BCS improves tissue conspicuity relative to TSC imaging. Future studies are needed to determine the value of \(^23\)Na MRI in delineating therapeutic responses in pediatric gliomas.

**Introduction**

Pediatric brain tumors are the most common cause of cancer death in infants and children. More advanced MRI techniques can provide added value in determining tumor response to treatment, but have similar limitations of inconsistency due to complex tumor microenvironments. Sodium concentrations, non-invasively measurable by sodium (\(^23\)Na) MRI, have been shown to be markers of tumor proliferation in animal glioma models and may be useful in monitoring posttreatment responses.\(^3, 4\) Increased sodium accumulation has also been seen secondary to other biological processes, including neuroinflammation, compromised mitochondrial metabolism and Na/K ATPase dysfunction.\(^5\) In adult CNS tumors, \(^23\)Na MRI has provided additional information related to cellular metabolism, complementary to standard proton (\(^1\)H) MRI.\(^6, 7\)
To our knowledge, $^{23}$Na MRI has not been evaluated in pediatric brain tumors. The primary aim of this study was to evaluate the feasibility of sodium MRI in measuring total sodium concentration (TSC) in both uninvolved brain tissues and three types of pediatric gliomas (DIPG, LGG, HGG). Our secondary aim was to determine the added value of imaging bound sodium concentration (BSC) as measured with the dual echo $^{23}$Na MRI, with respect to tissue conspicuity. The dual-TE imaging of BSC not only provides improved imaging conspicuity of lesions by suppressing the high CSF signal seen with single TE acquisition, but also is more reflective of intracellular sodium concentration. We quantitated serial changes in TSC and BSC, by utilizing voxel based, parametric mapping techniques.

**Materials And Methods**

This study was approved by the institutional ethics committee and informed consent was obtained in all cases.

**Participants**

Study participants were recruited from patients who were participating in glial-associated antigen peptide vaccine trials through the Pediatric Neuro-Oncology Clinic (RJ) at the Children's Hospital of Pittsburgh.

**Sodium MR Imaging Acquisition**

$^{23}$Na MRI images were acquired on a 3T Siemens Scanner (TIM Trio, Siemens AG, Erlangen, Germany) with a dual-tuned ($^1$H-$^{23}$Na) head volume coil (Advanced Imaging Research, Cleveland, OH). A custom-developed pulse sequence, twisted projection imaging (TPI), was used to acquire total sodium imaging data in all subjects with the following optimized single echo technique: FOV = 220mm, matrix size = 64x64x64, voxel size = 3.44mm (3D isotropic), TE = 0.5ms, TR = 100ms, averages = 4, and total acquisition time (TA) = 10min38sec. For a subset of patients, both total sodium and bound sodium imaging was calculated using a two-TE technique which was developed and implemented later in the study: FOV = 220mm, matrix size = 64x64x64, voxel size = 3.44mm (3D isotropic), TE$_1$/TE$_2$ = 0.5/5ms, TR = 100ms, averages = 4, and TA = 10min38sec for each TE.

**Post-processing and Quantitative Sodium MR imaging**

Baseline analysis: Intensity of the TE$_1$ and short-T$_2$ images was linearly calibrated using CSF region (TSC = 145 mM) and the noise-only background (TSC = 0 mM). Please refer to Supplemental Methods for details about calculation of sodium signal and additional serial analysis approach. The region of interest (ROI) quantification for normal appearing Grey Matter (GM) and White Matter (WM) for both TE$_1$ and short-T$_2$ images was performed. Follow-up sodium images were registered to the anatomical T2 or FLAIR proton images using 6 degrees of freedom rigid body transformation in medical imaging processing, analysis, and visualization (MIPAV). Intensity of all sodium images was normalized relative to that of vitreous fluid. Sodium concentration was then measured in the CSF, vitreous, uninvolved GM, WM, brainstem, and background noise, using uniform ROIs placed in these regions across the participants to
ensure sodium measurements were derived from a consistent volume. The primary site of tumors on sodium images were identified and manually segmented with the aid of the regular proton images.

**Statistical Analysis**

For the primary analysis, analysis of variance (ANOVA) was used to test difference in the total sodium concentration change among the tumor types at the primary lesion ROIs of the three groups. Additional ANOVA was performed among these groups for each of the uninvolved tissue regions (vitreous, CSF, grey matter, and white matter) (Supplemental Table 3). Linear regression was used to analyze the relationship between total sodium concentration in these regions and the age of the participant. An exploratory univariate regression analysis was performed to correlate serial changes in TSC (mM) with change in tumor volume (mm$^3$) as measured on concurrent conventional MRIs. An exploratory agreement analysis between serial change in TSC (mM) and conventional MRI response was calculated by performing a Cohen’s kappa. Possible sex-based difference in sodium concentration was also examined using the t-test on the mean TSC in the aforementioned ROIs. The false discovery rate controlling procedure method was used to correct for family-wise error in multiple comparisons.

**Results**

**Clinical Characteristics**

A total of 26 participants with gliomas were included in the cohort (median age of 12.0 years; range 4.9–23.3 years; 14 males): DIPG, (n = 11, median age of 8.8 years), recurrent supratentorial LGG (n = 6, median age = 16.5 years) and recurrent supratentorial HGG (n = 9, median age = 12.7 years) (Flow chart of participant recruitment displayed in Supplemental Fig. 1).

**Quantitative Total Sodium Concentration of Normal Brain and Brain Tumors**

Total sodium concentrations (mean +/- SD) were as follows: uninvolved (non-neoplastic) tissue: CSF = 126.6 +/- 11.3 mM, vitreous fluid = 99.8 +/- 14.9 mM, grey matter = 58.9 +/- 5.7 mM, white matter = 52.5 +/- 4.7 mM, and normal brainstem = 24.90 +/- 4.5 mM (Fig. 1-left) (Supplemental Table 3). An inverse relationship between TSC and age was observed in the GM (R = 0.53207; p-value = 0.0035), and WM (R = 0.50744; p-value = 0.0061) (Supplemental Fig. 2)(Supplemental Table 5). Compared to uninvolved brainstem (measured from portions of the uninvolved pons in participants with supratentorial LGG and HGG), DIPG s/p RT had significantly higher total sodium concentration (p < 0.0001) (Fig. 1, right; examples in Fig. 2). Among participants with recurrent LGG and HGG, the total sodium concentrations in the tumor were compared to their own uninvolved WM and GM measurements. For participants with recurrent supratentorial LGG and HGG, both groups exhibited higher total sodium concentration compared to their uninvolved WM and GM (p = 0.0005 WM and p = 0.0011 GM for LGG) and (p = 0.0042 for WM and p = 0.01781 for GM for those with HGG). (Fig. 1, right).
Serial Quantitative Intra-tumoral Total Sodium Concentration of Pediatric Glioma

Eight participants underwent serial $^{23}$Na MRI (total of 20 exams) to measure intratumoral TSC (Fig. 3, Supplemental Fig. 3–4)(Supplemental Table 4). The 8 patients include 1 with recurrent LGG, 4 with recurrent supratentorial HGG, and 3 with DIPG following the completion of RT. Six of these participants underwent only one follow-up sodium scan, while two patients with HGG underwent two to four follow-up scans. There was no change in TSC [within ± 1 SD mM] in 7/12 (58.3%) serial exams, increased in 2/12 (16.7%) serial exams, and decreased in 3/12 (25.0%) serial exams. As an exploratory analysis, we observed that while serial % change in TSC did not correlate with % change in concurrent tumor size, serial change in TSC did moderately agree with qualitative multi-modal conventional MRI treatment response assessment in an exploratory analysis (Supplemental Table 2).

Quantitative Intra-tumoral Bound Sodium Concentration of Pediatric Gliomas including Serial Imaging

Bound sodium concentration (vBSC) was measured in 5 patients who underwent the two-TE imaging. We computed vBSC for uninvolved GM (13.8 ± 8.67 mM) and uninvolved WM (14.1 ± 4.49 mM) falls within the accepted range for intracellular sodium in the brain (12–15 mM). Particularly for tumors near the ventricular system, the high sodium concentrations within CSF caused significant interference, which was overcome by doing subsequent evaluations using the dual-TE sodium MRI to measure BSC. The dual-TE sodium MRI suppresses the sodium signal within both CSF and necrotic foci, resulting in improved conspicuity of both non-neoplastic and neoplastic tissue located near peripheral cortex and ventricular CSF (Fig. 4 and supplemental Fig. 5). Among the group of eight patients that had serial TSC measurements, three patients had serial BSC measurements (Supplemental Table 4). In one case (Fig. 5A), a supratentorial HGG demonstrated no significant change in TSC at one month and four months after baseline sodium imaging, however, BSC did increase and correlated with the conventional imaging of tumor progression. The patient depicted in Fig. 5B demonstrated a decrease in TSC and BSC, two months after baseline sodium MRI, which correlated with a decrease in tumor volume on concurrent conventional MRI. The same patient in Fig. 5B demonstrated increased BSC in the region of evolving necrosis (Supplemental Fig. 5). Another patient with a HGG (Fig. 5C) had a concomitant decrease in TSC and BSC that correlated with a decrease in tumor volume (as measured on conventional MRI) nine months after sodium MRI baseline (Supplemental Table 2).

Discussion

This study has demonstrated the feasibility of performing $^{23}$Na MRI of brain tumors within the pediatric population and was able to distinguish uninvolved brain tissue from neoplastic glial tissue in pediatric patients. The total sodium concentration (TSC) for CSF, vitreous, GM, and WM in our study were similar to what has been reported in the adult literature$^7$. We did detect high TSC in both recurrent low- and high-
grade pediatric gliomas, which have distinctive histologies, suggesting that $^{23}$Na MRI may have less utility in assessing baseline tumor grade in contrast to serial assessment of therapeutic responses (future studies are warranted). $^{23}$Na MRI can assess metabolic changes in tissues, e.g. cell integrity and tissue viability with validated repeatability and reproducibility\textsuperscript{10, 11, 12-19}. The sensitivity of sodium imaging stems from the tightly controlled sodium ion homeostasis in healthy tissues which maintains a large concentration gradient between intracellular sodium concentration (ISC) at 10-15 mM and extracellular sodium at 145 mM. Importantly, TSC is elevated in tumors due to increased intracellular sodium (reflecting dysfunction of Na+-K+ pumps on the cell membrane) and/or an increased proportion of extracellular space (changes in cell morphology)\textsuperscript{20}.

Total sodium concentration in brain tumors can have limitations because of high sodium signal seen in CSF/necrosis that can mask intra-tumoral sodium signal that is related to proliferation. We show the added value of measuring volume-fraction weighted bound sodium concentration (as a proxy of BSC) with dual-TE imaging, which can saturate TSC-high sodium related signal in CSF/necrotic areas, providing better conspicuity of lesions relative to non-neoplastic structures. Dual TE $^{23}$Na MRI helped mitigate this limitation and potentially enhances its ability to determine heterogeneous treatment responses.

$^{23}$Na MRI is known to be a marker of tumor proliferation in animal glioma models and has shown utility in monitoring posttreatment necrosis and treatment responses in animals\textsuperscript{3, 4}. As such, we explored the relationship between quantitative serial TSC/ BSC measurement and both tumor volume and radiographic response assessment in a small sample of patients. Interestingly, we observed that while serial % change in TSC did not correlate with % change in concurrent tumor size, serial change in TSC did moderately agree with qualitative multi-modal conventional MRI treatment response assessment in an exploratory analysis. In contrast to serial TSC imaging, voxel-based parametric mapping of serial change in BSC did appear to be more reflective of the tumor response assessment within individual patients (in an exploratory analysis). We show that two patients with serial BSC serial changes were concordant with TSC and tumor volume as determined by conventional proton MRI. Studies have investigated the ability to differentiate bound sodium (thought to be reflective of intracellular sodium) and extracellular sodium with various techniques\textsuperscript{21, 22}. These studies are exploratory and future studies with a larger sample size are needed to further confirm these results.

The limitations of this study include the small number of heterogeneously treated tumor cases studied, which makes it difficult to compare between the groups of tumor types. For example, the DIPG cohort received radiation therapy 3-4 months prior to obtaining the sodium MRIs, which may cause a treatment related decrease in metabolic activity (lower TSC).

In conclusion, we demonstrate the feasibility of quantitatively evaluating $^{23}$Na by MRI in uninvolved brain tissue of pediatric glioma patients, with similar values to sodium concentrations seen in adults. Diffuse intrinsic brainstem gliomas post-RT and supratentorial gliomas demonstrated total sodium
concentrations (TSC) greater than adjacent uninvolved brain tissue. We also show the additional benefit of dual-echo Na MRI (bound sodium concentration) to improve visualization of tumor by distinguishing it from the surrounding tissue and CSF. Future studies are needed to determine the value of $^{23}$Na MRI in delineating response to treatment in pediatric gliomas.

**Abbreviations**

ANOVA = analysis of variance  
BSC = bound sodium concentration  
vBSC = volume-fraction weighted bound sodium concentration  
CNS = central nervous system  
CSF = cerebrospinal fluid  
DIPG = diffuse intrinsic brainstem glioma  
FLAIR = Fluid attenuated inversion recovery  
GAMs = glioma-associated microglia and monocyte-derived macrophages  
GM = Gray Matter  
HGG = high-grade gliomas  
IDH = isocitrate dehydrogenase  
ISC = intracellular sodium concentration  
LGG = low-grade gliomas  
MIPAV = medical imaging processing, analysis, and visualization  
MRI = magnetic resonance imaging  
RAPNO = Response Assessment in Pediatric Neuro-Oncology  
ROI = region of interest  
RT = radiotherapy  
TPI = twisted projection imaging  
TSC = total sodium concentration
WM = White Matter

References


**Figures**
Figure 1

Total sodium concentration (TSC) of the uninvolved cerebral tissue, vitreous humor, and cerebrospinal fluid (CSF), against the types of tumor. T-test comparing tumor grade ** = p<0.05; *** p<0.001. GM = grey matter, WM = white matter, DIPG = diffuse infiltrating pontine glioma, LGG = low-grade glioma, HGG = high-grade glioma.
Figure 2

Sodium MRI images demonstrating relative total sodium concentration (TSC) between three different types of pediatric gliomas. There is reduced relative TSC in the pediatric diffuse intrinsic pontine glioma (DIPG) compared to the supratentorial low-grade and high grade gliomas. There is no difference in relatively high TSC between the low-grade and high-grade gliomas.
Figure 3

Initial (top row) and follow-up (bottom row) sodium MRI scans of supratentorial pediatric gliomas with (A) increased total sodium concentration (TSC) corresponding to tumor progression in a supratentorial high-grade glioma (HGG), and (B) no change in TSC corresponding to a stable supratentorial low-grade glioma (LGG).
Figure 4

Serial total sodium MRI images at two different axial levels of a participant with supratentorial high-grade glioma treated with immunotherapy. This time-series demonstrates a decrease in TSC relative to uninvolved tissue, preceding the eventual lesion size reduction of the tumor (white arrow) as noted by fluid-attenuated inversion recovery (FLAIR) imaging (Supplemental Figure 3). Note a separate necrotic recurrent lesion (green arrow) also depicted in the sodium vBSC images (Supplemental Figure 5).
Figure 5

Two-TE sodium MRI showing tumor progression in high-grade glioma (Panel A [pt. ID 4027]), and response to therapy in supratentorial astrocytoma (Panel B [pt. ID 4010]) and in high-grade glioma (Panel C [pt. ID 4025]). In the tumor regions in the bound sodium images are pixels of vBSC value greater than 1 standard deviation (S.D.) from the average vBSC value (~22mM) over the tumor.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
• SupplementalMethods.docx
• SupplementalFigures.docx