

3D MRSI of Brain Neurochemical Changes in Breast Cancer Patients treated with Chemotherapy

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Introduction

Improvements in cancer screening and treatment have increased long-term survivorship and attention to survivors' daily functioning and quality of life. Therefore, studies of cognitive impairment related to breast cancer treatment have gained importance. Patients with breast cancer treated with chemotherapy have typically shown decreased neuropsychological performance [1, 2]. Although the mechanisms for the cognitive impairment caused by chemotherapy are not well understood, it is known that many chemotherapy agents are highly neurotoxic [3]. Investigation of the brain's metabolic response to chemotherapy can help to understand the specific pathophysiological mechanisms leading to cognitive and memory deficits. To date, only few studies have investigated metabolite levels and structural changes in white matter in high-dose chemotherapy patients [4, 5]. To our knowledge no study has reported measurements of metabolic changes in gray matter brain regions, although reduction of gray matter was found in breast cancer patients with systemic chemotherapy [6]. Here we used 3D proton magnetic resonance spectroscopic imaging (MRSI) to obtain metabolic information of hippocampus, thalamus and other brain regions in order to determine whether the reduction of gray matter changes is accompanied by neurochemical disturbances at detectable levels.

Materials and Methods

Participants were female breast cancer patients treated with (CTx+ group, N = 13) and without (CTx- group, N = 20) systemic chemotherapy and healthy controls (N = 12). All measures were completed at baseline (after surgery but before systemic treatment) and one month following the completion of chemotherapy MRI and MRSI data were acquired on a 3.0T Tim Trio (Siemens Healthcare) MRI scanner equipped with a standard 12-channel head coil array. Written informed consent was obtained for all subjects prior to participating in the study. MRI acquisitions included a T₁-weighted MPRAGE sequence (1x1x1.2 mm resolution) and T₂ axial images for planning of the MRSI acquisition. MRSI data were acquired using a standard 3D MRSI spin echo sequence with TR/TE = 1500ms/30ms, field of view = 120 x 120 x 96mm³, matrix size = 12 x 12 x 8 interpolated to 16 x 16 x 16, resulting in a nominal voxel size of 7.5 x 7.5 x 6 mm³. The PRESS slab was angulated parallel to the hippocampus as shown in Figure 1. The data were processed and analyzed using an in-house written pipeline. LCModel [7] was used for metabolite quantification. To date our MRSI analysis has been restricted to the hippocampus and thalamus: MRSI data were registered to T1-weighted images in order to obtain hippocampus and thalamus contributions for each voxel. The average concentrations relative to Cr and weighted by brain region contributions were calculated. The results were analyzed using SPSS (PASW statistics 18). Difference in metabolite levels between groups was explored using one-way ANOVA controlling for age. Any reported significance was adjusted for multiple comparisons. The paired Student t-test was used to test for differences within groups.

Results and Discussion

No significant cross sectional changes of metabolite levels were found between the three groups at either time point. Longitudinally, Cho/Cr in the left hippocampus ($p = 0.038$) and NAA/Cr in the left thalamus ($p = 0.015$) decreased significantly between the two visits in the CTx+ group. Additionally, a trend of increased ml/Cr ($p = 0.069$) was found in the left hippocampus between the two visits in the CTx+ group. Cho/Cr ($p = 0.047$) and ml/Cr ($p = 0.019$) were significantly decreased in the right hippocampus between the two visits for the CTx- group. Choline is a precursor for the neurotransmitter acetylcholine which is involved in many functions including memory and muscle control. A decrease of Cho/Cr levels over time found in both CTx+ and CTx- groups may indicate that these changes are not a specific response to chemotherapy treatment but may be related to breast cancer and its treatment in general. A decrease of NAA/Cr levels found only in the CTx+ group might be an indication of neuronal loss resulting from highly neurotoxic chemotherapy drugs. An increase of hippocampal ml/Cr levels is consistent with possible inflammatory changes or other dysfunction.

Conclusion

The detectable changes in brain metabolite levels in breast cancer patients treated with chemotherapy may help to explain part of cognitive dysfunction and complaints observed in cancer patients undergoing chemotherapy. Further investigations are needed to determine if these neurochemical changes are reversible.

References:

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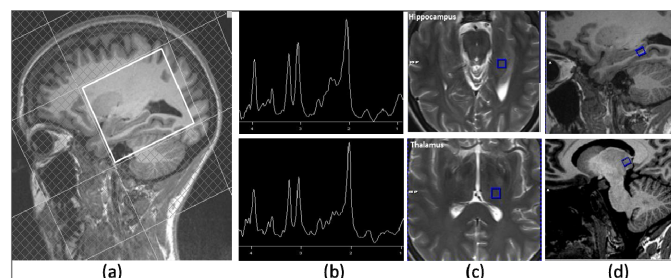


Figure 1. (a) PRESS slab placement (b) Representative spectra from hippocampus (top) and thalamus (bottom) and (c) locations of corresponding MRSI voxels.

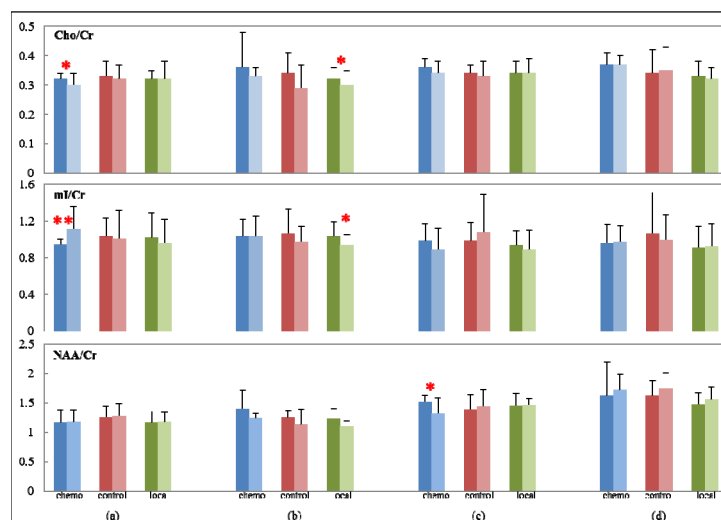


Figure 2. Comparisons between 2 visits in CTx+ (blue and light blue), control (red and light red) and CTx- (green and light green) groups. Left/right hippocampus and left/right thalamus were presented in column (a), (b), (c), (d), respectively. * represented $p < 0.05$ and ** represented $p < 0.1$