Brain Magnetic Spectroscopy Metabolites Correlate with Cerebrospinal Fluid (CSF) Mitochondrial DNA (mtDNA) Copy Number in Childhood with Acute Lymphoblastic Leukemia (ALL)

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Background

- In spite of excellent prognosis for childhood ALL, significant morbidity due to chemotherapy-related long term complications on neurocognition remain.
- The effects of ALL chemotherapy on brain and cognitive function are not well understood.
- Once chemotherapy-associated brain injury is recognized, it is often too late to intervene.

Objectives & Hypothesis

- To evaluate neurochemical levels and CSF mtDNA at baseline and one year post-initiation of chemotherapy in children with ALL.
- We hypothesize that biomarkers such as neurometabolites on 1H MR Spectroscopy (MRS) and levels of CSF mitochondrial DNA (mtDNA) may detect brain injury prior to cognitive deficits.

Design/Method

- 1H MRS of 3 brain regions (basal ganglia, frontal white matter, and frontal grey matter) was performed on newly diagnosed children (3-6 years old) with ALL at baseline (~6 weeks after induction therapy in ALL) and 1 year later.
- Neurocognitive testing was also performed at both time points.
- CSF cells, which were obtained from specimens collected during routine lumbar puncture as part of therapy, were assayed for mtDNA copy numbers.
- Regression analyses were performed to evaluate the relationship between MRS variables and log mtDNA numbers.

References

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[2] Kun L. E. Reddick W. E. Ogg R. J. Morris E. B. Pui C. H. Laningham, F. H. Childhood central nervous system leukemia. *Hematology Am Soc Hematol Educ Program*, pages 118–145, 2004.

[3] Foran T. Gofman I. Perin N. Schleimer S. Shiramizu B., Elbaggari A. Monitoring of cerebral spinal fluid by polymerase chain reaction in children with acute lymphoblastic leukemia. *International J Ped Heme/Onc*, 5:475–483, 1998.

Results

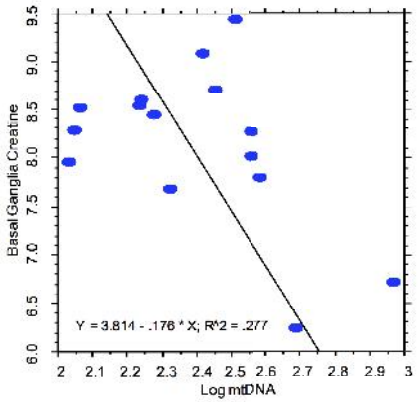

Figure 1: Regression plot showing creatine levels and log mtDNA copy number

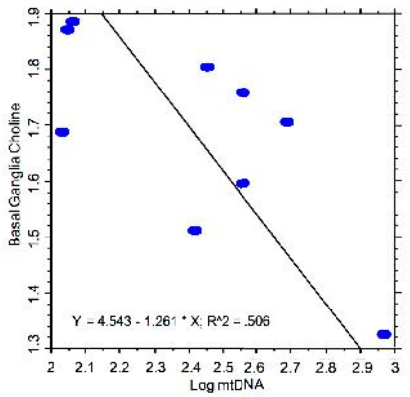

Figure 2: Regression plot showing choline levels and log mtDNA copy number

- Nine children with ALL were enrolled and studied at baseline and ~1 year later.
- MtDNA numbers correlated with basal ganglia choline (Cho) levels at baseline only (p=0.04), and total creatine (Cr) levels at both time points (p=0.04).
- Cognitive performance was appropriate for age at both time points for all of the children and all children remain in clinical remission through the first 12 months of therapy.

Discussion

- Choline and creatine levels in the brain reflect neuronal injury and change over time in children receiving chemotherapy for ALL.
- CSF mtDNA copy numbers may reflect a survival phenotype or injury from chemotherapy of leukemic cells in the brain.
- The appropriate-for-age neurocognitive test results at both time points, in spite of the changes noted in mtDNA, basal ganglia Cho, and basal ganglia Cr, suggest that the biomarkers may be more sensitive to neuronal injury than neurocogntive testing.

Conclusion

- Choline and creatine levels are thought to be surrogate markers of brain injury.
- The association between mtDNA, choline, and creatine levels suggests greater injury to the basal ganglia in those with more severe disease, especially in the early phase of ALL.

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