ANTIOXIDANT ENZYME POLYMORPHISMS AND NEUROPSYCHOLOGICAL OUTCOMES IN MEDULLOBLASTOMA SURVIVORS: A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY (CCSS)

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Purpose: Psychological or neurocognitive impairment is often seen in medulloblastoma survivors after craniospinal radiation, however, which patients will be significantly impaired cannot be predicted in advance. Given that radiation exerts its effect through free radical generation, we investigated the role of antioxidant enzyme polymorphisms in predicting this outcome, and hypothesized that patients who had polymorphisms associated with lower free radical scavenging enzyme function would have higher occurrence of impairment.

Method: We identified 109 medulloblastoma survivors from the CCSS cohort who completed the CCSS Neurocognitive Questionnaire (NCQ), the Brief Symptom Inventory-18 (BSI-18), and provided buccal DNA samples. We used real-time PCR allelic discrimination assays to determine SOD2 (rs4880), GPx1 (rs1050450), and GSTP1 (rs1695 and rs1138272) polymorphisms and PCR for GSTM1 and T1 gene deletions. We used univariate and multivariable ANOVA to examine the association between NCQ subscale (task efficiency, emotional regulation, organization, memory) or BSI-18 subscale (depression, anxiety, somatic complaints, global severity) scores, and genotypes or clinical factors, including age at diagnosis, gender, and radiation dose.

Results: Patients less than 7 years old at diagnosis displayed more problems with task efficiency ($p<0.00001$) and less problems with somatic complaints ($p=0.004$) than patients 7 years or older. Females reported more organization problems than males ($p=0.02$). Patients with homozygous GSTM1 gene deletion reported higher anxiety (mean null genotype= 47.3 ± 9.2, non-null= 43.9 ± 7.8; $p=0.04$), more depression (null= 51.0 ± 9.8, non-null= 47.0 ± 9.4; $p=0.03$), and more global distress (null= 50.2 ± 9.7, non-null= 45.2 ± 9.9; $p=0.01$). All associations for the GSTM1 polymorphism remained statistically significant across multivariable models controlling for age, gender, and radiation dose.

Conclusion: Homozygous GSTM1 gene deletion was consistently associated with greater psychological distress in medulloblastoma survivors across multiple domains. There is no data explaining which antioxidant enzymes are involved in clearing radiation induced free radicals. GSTM1 may be an important enzyme for such function, although further studies are needed to explore this possible mechanism.