Effects of Hydroxyurea on Brain Function in Children with Sickle Cell Anemia

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Abstract

Introduction: Sickle cell anemia (SCA) results in numerous adverse effects on the brain, including ischemic lesions and neurocognitive dysfunction. Hydroxyurea has been utilized extensively for management of SCA, but its effects on brain function have not been established. Methods: We examined prospectively the effects of one year of treatment with hydroxyurea on brain function in a cohort of children with SCA (HbSS/HbSβ0-thalassemia) by baseline and exit evaluations, including comprehensive neurocognitive testing, transcranial Doppler ultrasound (TCD), and brain MRI [silent cerebral infarcts (SCI), gray matter cerebral blood flow (GM-CBF), and blood oxygen level dependent (BOLD) signal from visual stimulation]. Results: Nineteen patients with SCA, mean age 12.4 years (range 7.2-17.8), were evaluated. At baseline, subjects had these mean values: full scale IQ (FSIQ) 81.9, TCD velocity 133 cm/sec, GM-CBF 64.4 ml/100g/min, BOLD signal 2.34% increase, and frequency of SCI 47%. After one year of hydroxyurea, there were significant increases in FSIQ (+2.8, p=0.036) and reading comprehension (+4.8, p=0.016), a significant decrease in TCD velocity (-11.4 cm/sec, p=0.007), and no significant changes in GM-CBF, BOLD, or SCI frequency. Furthermore, FSIQ was associated with higher hemoglobin F (HbF) and lower GM-CBF, but not with hemoglobin level. Discussion: Significant improvement of neurocognition and decreased TCD velocity following one year of treatment support the use of hydroxyurea for improving neurocognitive outcomes in SCA. Understanding the mechanisms of benefit, as indicated by relationships of neurocognitive function with HbF, hemoglobin, and CBF, requires further evaluation.

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Dr. Peter Newburger, Editor in Chief, Pediatric Blood and Cancer:

We would appreciate your review of "Effects of Hydroxyurea on Brain Function in Children with Sickle Cell Anemia" by Drs. Wang, Zou, Hwang, Kang, Ding, Heitzer, Schreiber, Helton and Hankins for publication as a Research Article in PBC.

Our study is the first to study the effect of treatment with hydroxyurea on brain function in children with sickle cell anemia using a comprehensive evaluation, which included both neuropsychologic assessment and functional MRI. Evaluations were performed immediately before and at the end of one year of treatment with hydroxyurea. Treatment led to significantly increased full scale IQ score and reading comprehension

and decreased transcranial Doppler velocities. Full scale IQ was associated with higher Hemoglobin F and lower cerebral blood velocity. These data provide further support for the use of hydroxyurea in children with sickle cell anemia because of its enhancement of brain function.

This manuscript has not been submitted elsewhere nor previously published. The authors do not have any conflicts of interest. All authors have contributed to the manuscript in significant ways and have reviewed and agreed upon the manuscript content.

Potential reviewers: Dr. Alison King (Washington University), Dr. Daniel Armstrong (University of Miami), Dr. Charles Quinn (University of Cincinnati). There are no excluded reviewers.

Thank you for your consideration. Sincerely,

Winfred C. Wang, MD

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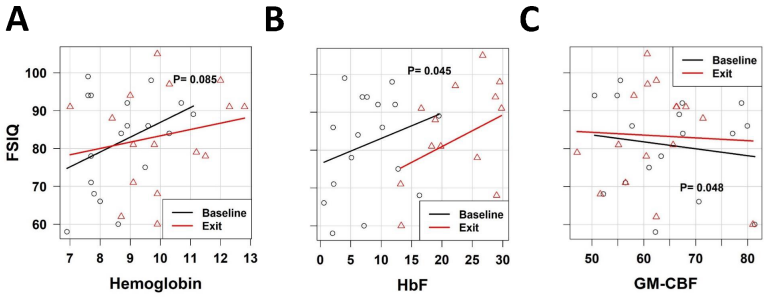

Figure 1. *Factors Influencing FSIQ.* Scatterplot of FSIQ versus hemoglobin (Panel A), HbF (B) and GM-CBF (C) by baseline and exit time points. Abbreviations: FSIQ=Full Scale Intelligence Quotient, HbF=hemoglobin F, GM-CBF=gray matter cerebral blood flow. P values were calculated to test the main effect on FSIQ of hemoglobin, HbF or GM-CBF from linear mixed effects models with adjustment for age.