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Improvement in Processing Speed Following Haploidentical Bone Marrow Transplant with Post-Transplant Cytoxan in Children and Adolescents with Sickle Cell Disease

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To the Editor:

Children and adolescents with sickle cell disease (SCD) are at significant risk for cerebral infarction and neurocognitive deficits. In a quantitative meta-analysis, Prussien et al. (2019) showed that school-aged children with SCD display significant deficits in full scale IQ, verbal reasoning, perceptual reasoning, executive function, and processing speed relative to the normative mean in sibling and healthy controls, with mean standard scores ranging from 82.38 to 87.51. Quantitative reviews have also found that deficits in cognitive function in this population increase with age.^{1,2}

Few studies have investigated whether therapeutic interventions to prevent cerebral infarction impact progressive neurocognitive benefits in individuals with SCD. Three published studies to date have assessed the effect of bone marrow transplantation (BMT) on cognition in SCD, and findings show that full scale IQ remained stable after transplant.³⁻⁵ King et al. (2019), also found that verbal IQ and performance IQ also remain stable. However, these findings are based on very small samples, and replication is necessary across multiple domains of cognition including various transplant approaches. The current study aimed to assess the effect of BMT across multiple domains of neurocognitive function in

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children and adolescents with SCD. We hypothesize that successful related haploidentical BMT (haplo-BMT) in individuals with SCD will result in stable to improved neurocognitive function.

A select cohort of patients underwent reduced intensity conditioning haplo-BMT with post-transplant cytoxan for SCD as part of an international learning collaborative. Only participants with pre- and post-transplant cognitive assessments were included in analyses.⁶ The transplant data base and electronic patient records were used to assess baseline demographics and transplant-related outcomes. All patients received a common conditioning regimen of fludarabine, cytoxan, thiotepa, and rabbit anti-thymocyte globulin along with 200 cGy total body irradiation followed by infusion of unmanipulated bone marrow grafts from related haploidentical donors that were at least 5/10 human leukocyte antigen matched.⁶ Graft-versus-host-disease prophylaxis included post-transplant cytoxan along with sirolimus and mycophenolate mofetil.⁶ Neurocognitive assessments were conducted 2–3 months prior and 12 months post-transplant. All participants were administered age-appropriate Wechsler scale of intelligence (i.e., Wechsler Intelligence Scale for Children – Fourth Edition for children ages 6 to 16 years and the Wechsler Adult Intelligence Scale – Fourth Edition for adolescents over age 18 years). Repeated measures t-tests were used to assess pre-post changes in neurocognitive function, and multivariate linear regressions were conducted to assess the effect of participant age at transplant on post haplo-BMT scores two-tailed $p < 0.05$ required for significance.

Sixteen children and adolescents with sickle cell anemia (Hb SS) had both pre- and post-haplo-BMT cognitive assessments. Mean age at transplant was 10.75 years and ranged from 6 to 18 years. Indication for transplant included silent cerebral infarct 63% (10/16), stroke 56% (9/16), and both silent infarct and stroke in 50% (8/16). Twenty-five percent (4/16) of participants had neither stroke or silent infarct, and 50% (8/16) had abnormal transcranial Doppler velocity (> 200 cm/sec) pre-transplantation. All patients fully engrafted (100% myeloid cells by day +100), though two had secondary graft failure at days +60 and +600, respectively. No participant developed grades III-IV acute or extensive chronic graft-versus-host disease.

Findings from repeated measures t tests (Table 1) showed no significant difference in mean scores pre- and post-transplant in verbal reasoning (pre = 91.44, post = 90.69, $d = .09$, $p = .641$), perceptual reasoning (pre = 91.56, post = 86.12, $d = .57$, $p = .066$), working memory (pre = 93.56, post = 86.19, $d = .46$, $p = .158$), and full scale IQ (pre = 84.50, post = 86.00, $d = .20$, $p = .694$); however, mean scores for processing speed were significantly greater post-transplant relative to pre-transplant (pre = 79.81, post = 86.31, $d = .49$, $p = .023$). Results also show that despite disease severity, the current sample of adolescents demonstrated greater scores in verbal reasoning, perceptual reasoning, and executive function at both timepoints relative to prior meta-analytic findings for school-aged children.¹ Findings from multivariate linear regressions showed that participant age at transplant significantly predicted higher scores in processing speed post Haplo-BMT while controlling for pre-transplant scores ($\beta = .40$, $p = .048$). For every increased year in age at transplant the standard score for processing speed post haplo-BMT improved 1.67 points. Age at transplant was not a significant predictor of the other neurocognitive domains assessed.

The current study has replicated and extended findings on the effect of BMT on neurocognitive function in children with SCD using the largest sample to date. Findings suggest that neurocognitive function outcomes are stable to improved following haplo-BMT with post-transplant cytoxan in children and adolescents with SCA. Prior studies assessing the effect of BMT on neurocognitive function have used broad composites of intelligence, verbal IQ, and performance IQ. Our analyses across multiple specific domains of neurocognitive functioning has highlighted the specific effect of BMT on processing speed in particular. Further, this sample obtained higher neurocognitive scores relative to meta-analytic findings in this population, which suggests that socio-environmental inclusion criteria for haplo-BMT might favor patients with higher neurocognitive function relative to the average child with SCA. Finally, the literature shows that adults with SCD display the greatest neurocognitive deficits in processing speed¹, meaning the positive association of participant age with this domain post haplo-BMT is particularly important.

Future studies should evaluate long-term neurocognitive function outcomes in SCD patients undergoing haplo-BMT compared to age- and socio-environmentally matched cohorts on best supportive care.

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Table 1.

Multivariate analysis of different cognitive domains pre- and post-transplant

	M (SD)				
	N	Pre BMT	Post BMT	Cohen's <i>d</i>	<i>p</i> Value
Verbal Reasoning	16	91.44 (8.41)	90.69 (8.99)	.09	.641
Perceptual Reasoning	16	91.56 (8.02)	86.12 (10.80)	.57	.066
Working Memory	16	93.56 (15.75)	86.19 (15.98)	.46	.158
Processing Speed	16	79.81 (12.29)	86.31 (14.04)	.49	.023
Full Scale IQ	8	84.50 (5.93)	86.00 (8.57)	.20	.694