POTENTIAL MEDICAL APPLICATIONS OF TRANSCRANIAL DOPPLER VELOCITIES IN CHILDREN WITH SICKLE CELL DISEASE

by

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A Senior Honors Project Presented to the

Honors College

East Carolina University

In Partial Fulfillment of the

Requirements for

Graduation with Honors

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May 2017

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Abstract

Although it is a topic of importance, research is scarce concerning renal dysfunction in pediatric sickle cell patients. Elevated blood pressure, increased urinary protein, and other signs and symptoms of early chronic kidney disease (CKD) are commonly found in children with sickle cell disease (SCD); the purpose of this study was to investigate a potential method for detecting renal dysfunction and the signs of CKD in children before the problem escalates. Transcranial Doppler (TCD) is a method used in sickle cell patients to determine their risk of stroke. It has to be presumed that in addition to CNS vasculopathy, SCD cause vasculopathy in other organs. It is not clear if there is a relationship between TCD velocity and renal damage. The purpose of this study was to investigate the relationship between TCD values and renal function. After obtaining appropriate institutional review board (IRB) approval, a retrospective chart review of 90 pediatric sickle cell patients managed at Vidant Medical Center, in Greenville in North Carolina was performed, to test the use of TCD in detecting dysfunction in the renal system. Statistical analysis was then completed to evaluate the relationship between these variables. The renal values collected were serum creatinine (SCR) and urine creatinine (UCR), blood urea nitrogen BUN, and Albumin/Creatinine Ratio (ACR); these renal values were individually analyzed. The TCD values collected consisted of the maximum velocities of the right middle cerebral artery (rMCA), left middle cerebral artery (lMCA), right internal carotid artery (rICA), and left internal carotid artery (l ICA). Based on their TCD values, patients were categorized as normal, conditionally abnormal, or abnormal. There was a *statistically significant difference* in the SCR values across the three subject groups, however, this finding may be questioned when age is factored into this variable. The results indicate that BUN, UCR, and ACR cannot be used to determine if TCD velocities are a useful tool in the early detection of renal dysfunction in patients with sickle cell disease. However, lower SCR values were seen in patients with higher TCD velocities, therefore the use of TCD values to detect renal dysfunction should not be ruled out based on this study.

Introduction

Prevalence of Sickle Cell Disease

Sickle cell disease is a recessive condition affecting about 100.000 individuals in the United States and millions worldwide. According to a survey conducted by the Centers for Disease Control and Prevention (CDC) and the National Institutes for Health (NIH)'s, National Heart, Lung, and Blood Institute (NHLBI) in 2008, Sickle Cell Disease (SCD) occurs in approximately 1 out of every 1,435 births in North Carolina. From 2004-2008. Approximately 5,578 residents of North Carolina were reported to have SCD. Out of those 5,578 residents around 2,175 were under the age of eighteen.[1]

Sickle Cell Disease Pathophysiology

Sickle Cell Disease is caused by a mutation in the beta-globin gene. The 17th nucleotide is altered from thymine to adenine. The sixth amino acid of that beta-globin then becomes valine, a hydrophobic amino acid, instead of hydrophilic glutamic acid. This creates what is called a "S" mutation.[2] When this

mutant hemoglobin is deoxygenated it becomes extremely insoluble and rigid causing damage to the membrane of the red blood cells (RBCs) and adhesion of the RBCs to the endothelium of the blood vessel wall [Figure 1]. This RBC damage and adhesion can cause repeated vascular occlusion, anemia, acute chest syndrome (ACS), stroke, pain crisis, and eventually organ damage, including renal damage.[3]
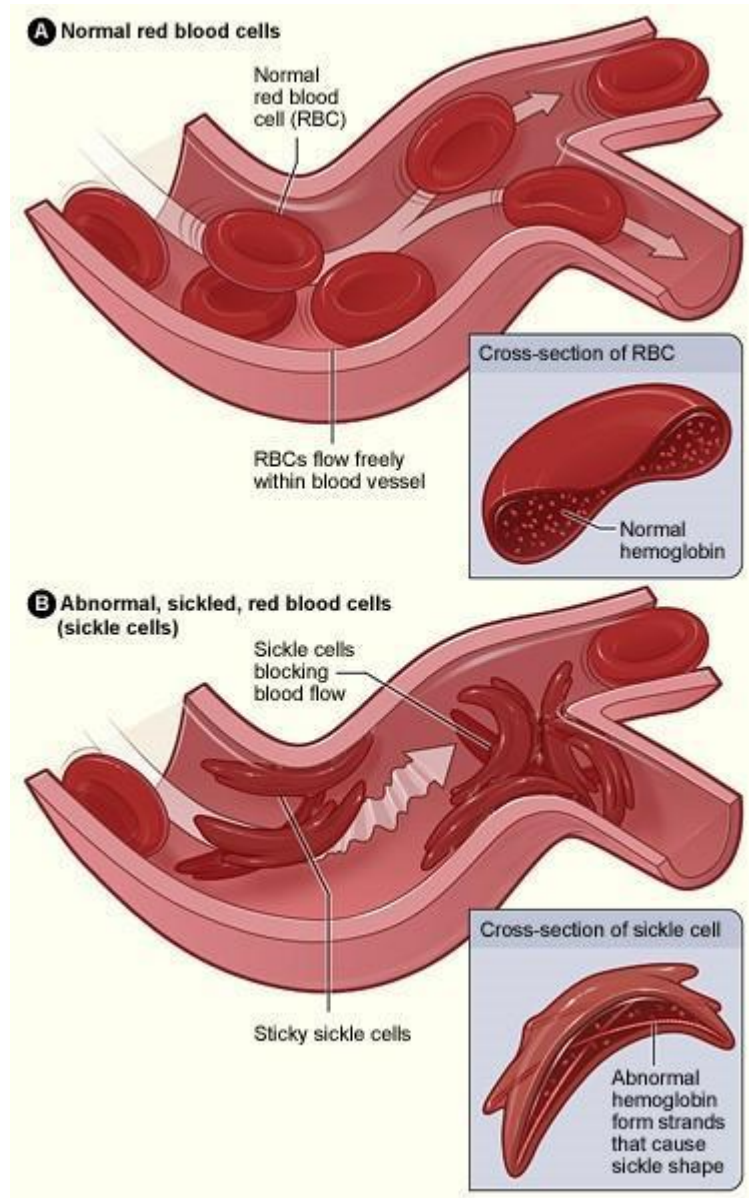

Figure 1 Virtual representation of a blood vessel containing

normal red blood cells and a blood vessel containing sickled,

red blood cells.[11] From this figure, the vasoocclusion occurring due to sickled red

blood cell can be seen.

Renal Dysfunction

The organs that are most commonly affected by SCD are the spleen, lungs, kidneys, liver, and brain.[3] Mutant hemoglobins are likely to polymerize in the renal medulla because that area has a low partial pressure of oxygen, low pH, and osmolality is high causing dehydration of the RBCs.[4]

The four renal values that were extracted for analysis were SCR, BUN, UCR, and ACR. Serum creatinine, or SCR, tends to be significantly lower in children with SCD because children with SCD have a high glomerular filtration rate (GFR) and exhibit hypersecretion of creatinine. In addition, these patients tend to have a lower muscle mass. The interpretation of serum creatinine must take this into account. Values near the low end of the normal range should increase suspicion for impaired renal function.[5] Elevated blood urea nitrogen (BUN) levels are associated with an increased risk of death in children.[6] Urine creatinine (UCR) measures the amount of creatinine excretion. Lastly, urine albumin: creatinine ratio (ACR), when combined with GFR can support the early detection of renal dysfunction.[7]

30% of adults with SCD develop chronic renal failure; it is a common cause-of-death in the sickle cell population.[8] The early symptoms for this disease (hyperfiltration, elevated blood pressure, proteinuria, etc.) are often seen in children.[9] If no precautionary measures are taken to reduce the demand placed on the kidneys of that child, these initial complications can develop into full CKD in adulthood. Currently, there is no validated tools to screen for early kidney dysfunction in pediatric sickle cell patients and research in this area is severely deficient. Therefore, it is essential to develop a method to detect kidney damage early in patients with SCD.[3] Given the pathophysiology behind sickle cell disease and the effect it has on circulation, it is worth investigating whether a correlation can be found between transcranial and renal blood flow and if this is related to renal dysfunction in patients with SCD. Abnormal renal blood flow may cause renal damage or dysfunction that may be evident in the patient's laboratory values pertaining to their renal function.

Transcranial Doppler Ultrasonography

Transcranial Doppler (TCD) ultrasonography is used to successfully detect intracranial artery stenosis, or narrowing of the blood vessels, in patients with SCD.[10] Research has shown that an increase in TCD velocity in the cerebral arteries is correlated with an increase in stroke risk. Therefore, the purpose of this study was to assess the relationship between TCD velocities and values used to assess renal function (SCR, BUN, UCR, and ACR). TCD is safe and acceptable for use on children with a relatively low cost.[10] TCD velocities for the right and left middle cerebral artery (rMCA and lMCA) and the right and left internal carotid artery (rICA and l ICA) were extracted because the majority of the patients had values for these four arteries. Recommendations for TCD velocities differ slightly depending on the source, however, Adams *et al.* were able to establish a threshold for abnormal blood flow velocity in SCD patients that can be generally agreed upon.[10] The established level is forty to fifty percent higher than the average velocity for SCD patients without anemia.[10] The threshold established for abnormal

blood flow velocity is greater than or equal to 170 centimeters per second (cm/s).[10] From this threshold, three classification groups were defined for the subjects based on their TCD values. If all four values were less than 130 cm/s, the subject was classified as normal. If one or more of the four values were within the range of 130-169 cm/s and none of the values were greater than 170 cm/s, the subject was classified as conditionally abnormal. Lastly, if one or more of the values was greater than or equal to 170 cm/s, the subject was classified as abnormal.

It is reasonable to hypothesize that abnormal transcranial blood flow may indicate abnormal renal blood flow because the organ systems are interrelated and rely heavily on the body's blood composition and the blood vessels' vasculature. The purpose of this study was to establish whether there is a correlation between abnormal transcranial blood flow velocity, abnormal renal laboratory values, and evidence of renal dysfunction in patients with sickle cell disease.

Methods

Ethical Considerations

All of the data in this study contained no patient identifiers and was collected using a retrospective chart review. A separate code sheet was kept as an index of which patients were used in this study. Therefore, it was not necessary to obtain consent from the patient prior to assessing the relevant patient charts. Prior to any data collection, approval for the study was obtained from East Carolina University's Institutional Review Board. All data pertaining to this study and the code sheet were stored on the Department of Hematology/Oncology's Pirate Drive throughout the course of this study.

Patient Population and Data Extraction

A retrospective chart review was completed using a pool of patients seen by the doctors in the Pediatric Hematology/Oncology Department at Vidant Medical Center in Greenville, NC. Ninety total patients, 2-16 years old, were selected for the study based on whether they had the majority of the necessary data values. Forty-seven out of ninety patients in the study were female and forty-three were male. In order to be included in the study, the subject must have had all four TCD velocities in order to be included. Thirty patients with normal TCD velocities, thirty patients with conditionally abnormal TCD velocities, and thirty patients with abnormal TCD velocities were selected. In the data file, subjects were coded with a number. A separate code sheet was created for each subject's name, date of birth, and their subject number. Once the data was extracted for all ninety subjects, the full dataset was analyzed for any errors during extraction.

Statistical Analysis

Statistical analysis was completed using IBM SPSS software. The subjects were categorized by TCD condition as abnormal, conditionally abnormal, and abnormal. ACR values were also categorized as normal, moderately increased, and severely increased. Twelve scatter plots were generated. Four scatter plots each were generated to compare each of the renal values (SCR, BUN, and UCR) to the individual TCD velocities extracted: rMCA, rICA, l MCA, and l ICA. Three side-by-side boxplots were generated depicting the SCR, BUN, and UCR values within the three TCD conditions. The side-by-side boxplot of SCR vs. TCD condition can be seen in Figure 2. Four scatter plots were generated depicting ACR condition (no data, normal, moderately increased, or severely increased) versus the individual TCD velocities: rMCA, rICA, l MCA, and l ICA. A One-way ANOVA was then used to determine if there was a significant difference in the renal values from one TCD group to another, the results are in Table 1.
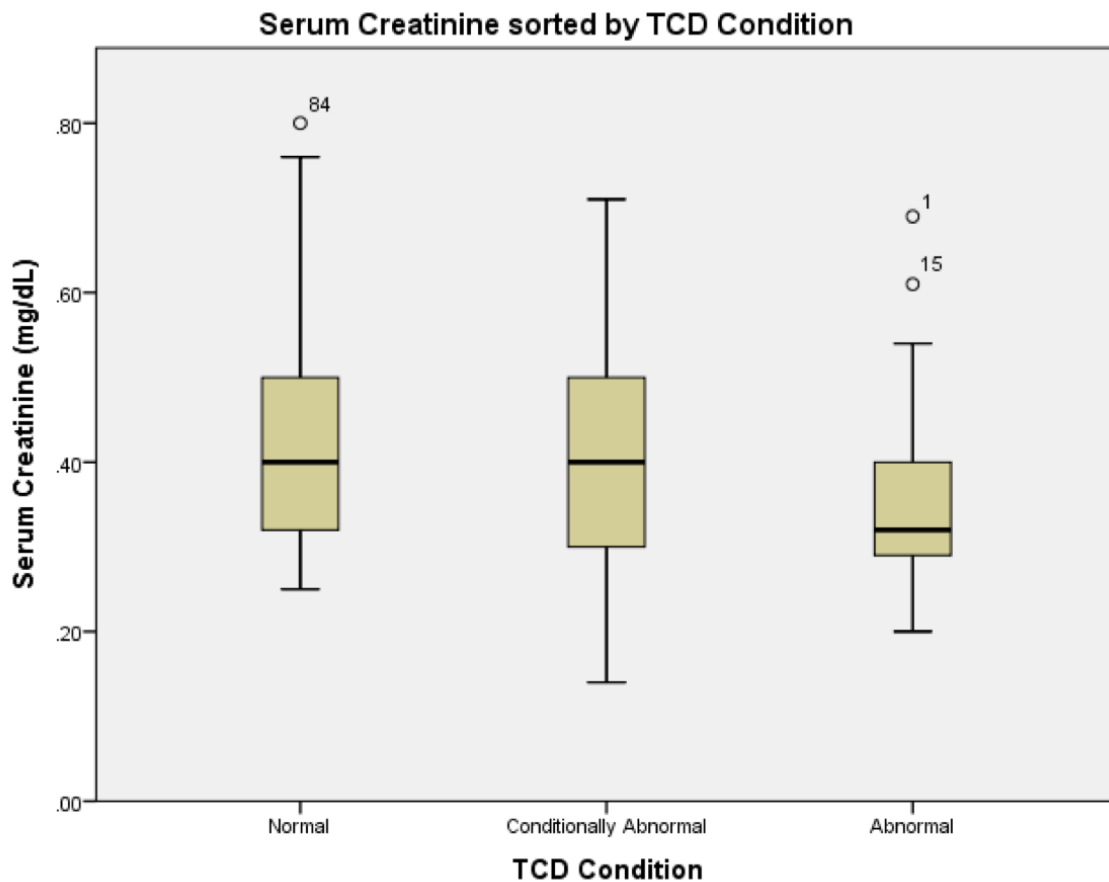

Figure 2 Serum Creatinine values sorted by TCD condition. From this figure, it can be

observed that as TCD velocity increased, serum creatinine decreases.

ANOVA

	df	p-value
Serum Creatinine (SCR)	2	0.041
Blood Urea Nitrogen (BUN)	2	0.118
Urine Creatinine (UCR)	2	0.440

Table 1 Anova results of SCR, BUN, and UCR comparative analysis. From the p-value, significant difference can be seen in the SCR values across the three TCD conditions.

Results

Participants

Only patients with sickle cell disease and documented TCD velocities in all necessary vessels as well and renal function studies were included. However, no patients with systemic disease were included in the study due to the fact that this could cause a change in their renal values. Only patients with diagnosed SCD who are 2-16 years old were included since this is the age group routine screened using TCD. Forty-seven out of ninety patients in the study were female and forty-three were male. There was not a very large pool of patient who has all of the qualifying information that were not included in the study.

Statistical Results

The results of the study indicate that there is *no significant difference* in the BUN and UCR values across the three TCD conditions, with p-values of 0.118 and 0.440 respectively, and no trends can be seen in the graphs generated to assess the changes in ACR. However, there was *a significant difference* in the SCR values across the three TCD conditions (p-value=0.41). Subjects with higher TCD velocities, particularly high rMCA velocities, tended to have lower SCR values. As a reminder, those with renal dysfunction, typically have lower SCR values. There are three outliers to this trend. One subject in the normal TCD condition and two subjects in the abnormal TCD condition were found to have SCR values above their group counterparts.

Conclusion

The results indicate that BUN, UCR, and ACR should not be used to test if TCD velocities can be used as a tool in the early detection of renal dysfunction in patients with sickle cell disease. However, lower SCR values were seen in patients with higher TCD velocities, with a few exceptions, which suggests that TCD velocities should not be completely ruled out based on this study. One of the limitations of this study was the small pool of patients included in this study, however, this was the first stage of a larger study and it was an appropriate as a starting point. In order to determine further if TCD velocities can be used as a tool in the early detection of renal dysfunction in patients with SCD, other renal values that are better known to be better predictors of renal dysfunction, such as cystatin-C and *N*-acetyl-B-D-glucosaminidase, should be collected as well. This may be difficult since these values are not routine checked during comprehensive sickle cell management visits and must be specifically collected in order to be analyzed.

References

1. "Sickle Cell Disease in North Carolina." Registry and Surveillance System for

   Hemoglobinopathies. *Centers for Disease Control and Prevention, National Institutes for Health,*

   and National Heart, Lung, and Blood Institute. Web. 20 Oct. 2015

2. Rees, David C., MD, Thomas N. Williams, MD, and Mark T. Gladwin, MD. "Sickle-cell Disease."

Lancet 376.1 (2010): 2018-031. *ProQuest Health and Medical Complete*. Web. 20 Oct. 2015.

3. Sarnaik, Sharada A. "Sickle Cell Diseases: Current Therapeutic Options and Potential Pitfalls in

    Preventive Therapy for Transcranial Doppler Abnormalities." *Pediatric Radiology* 35.3 (2005):

    223-28. *ProQuest Health and Medical Complete*. Web. 20 Oct. 2015.

4. Scheinman, J.I. Sickle cell disease and the kidney. National Clinical Practice of Nephrology

    (2009); 5:78-88. Web. 30 Jan. 2017.

5. Aloni, Michel Ntetani, René Makwala Ngiyulu, Jean-Lambert Gini-Ehungu, Célestin Ndosimao

    Nsibu, Mathilde Bothale Ekila, François Bompeka Lepira, and Nazaire Mangani Nseka. "Renal

    Function in Children Suffering from Sickle Cell Disease: Challenge of Early Detection in Highly

    Resource-Scarce Settings." *PLoS ONE* 9.5 (2014): n. pag. *ProQuest Health and Medical Complete*.

    Web. 20 Oct. 2015.

6. Costa, S., & Fisher, S. L. (2012). BMI, BUN may predict death from diabetic ketoacidosis in

    children. *Endocrine Today, 10*(5), 16-17. Retrieved from

    http://search.proquest.com.jproxy.lib.ecu.edu/docview/1014003418?accountid=10639

7. Hoefield,Richard A., Kalra, Philip A., Baker, Patricia G., Sousa, Ines, Diggle, Peter J., Gibson,

    Martin J., O'Donoghue, Donal J., Middleton, Rachel J., New, John P.; The use of eGFR and ACR to

    predict decline in renal function in people with diabetes. *Nephrol Dial Transplant* 2011; 26 (3):

    887-892. doi: 10.1093/ndt/gfq526

8. Platt, O. S., Brambilla, D. J., Rosse, W. F., et al. Mortality in sickle cell disease. Life expectancy

    and risk factors for early death. New England Journal of Medicine (1994); 330: 1639-44.

9. Bodas, Prasad, Alex Huang, Mary O'Riordan, John R. Sedor, and Katherine Dell. "The Prevalence

    of Hypertension and Abnormal Kidney Function in Children with Sickle Cell Disease –a Cross

    Sectional Review." *BMC Nephrology* 14.1 (2013): 237-42. *ProQuest Health and Medical*

    Complete. Web. 20 Oct. 2015.

10. Adams, Robert, Virgil Mckie, Fenwick Nichols, Elizabeth Carl, Dao-Long Zhang, Kathy McKie, Ramon Figueroa, Mark Litaker, William Thompson, and David Hess. "The Use of Transcranial Ultrasonography to Predict Stroke in Sickle Cell Disease." *New England Journal of Medicine N Engl J Med* 326.9 (1992): 605-10. *ProQuest Health and Medical Complete. Web*. 20 Oct. 2015.

11. National Heart, Lung, and Blood Institute. (2016). What is sickle cell disease?. [Figure 1]. Retrieved from https://www.nhlbi.nih.gov/health/health-topics/topics/sca