Journal of the American Society of Hypertension ■(■) (2018) 1–9

Research Article

Ambulatory hypertension in a pediatric cohort of sickle cell disease

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Manuscript received January 25, 2018 and accepted April 19, 2018

Abstract

Hypertension is an established risk factor for subsequent cardiovascular and renal disease in children as well as adults. Sickle cell disease (SCD) is a genetic disorder associated with chronic hemolytic anemia with the major manifestation of vaso-occlusive crises. Although this disease entity involves most organ systems causing vascular and pulmonary injury, little is known about blood pressure (BP) levels or prevalence of hypertension in children with SCD. A cross-sectional study was conducted on 56 children with SCD (54 with hemoglobin SS disease; 2 with hemoglobin Sβ^0 thalassemia; 29 females). Study participants underwent 24-hour ambulatory BP monitoring (ABPM). Serum creatinine and cystatin C were obtained to assess estimated glomerular filtration rate with age-based formulas. A random urine sample was obtained to estimate urine osmolality and urine albumin to creatinine ratio. Mean age range was 11.9 (±4.5) years. Seventeen participants (30%) met criteria for hypertension based on ABPM. Of the 17 participants classified with hypertension, three had office hypertension with ambulatory hypertension, and 14 had masked hypertension detected on ABPM. Another 28 participants (50%) had some abnormal ABPM parameters in the form of either prehypertension and/or lack of normal nocturnal dipping status. The prevalence of confirmed hypertension, largely manifest by masked hypertension, is high in children, as young as 6 years of age with SCD. Early identification of hypertension in SCD children can confer benefit as it is an important modifiable risk factor for progression of cardiovascular and renal disease. J Am Soc Hypertens 2018;■(■):1–9.

Keywords: Ambulatory blood pressure monitoring (ABPM); blood pressure (BP); chronic kidney disease (CKD); sickle cell disease (SCD).

Introduction

Sickle cell disease (SCD) is a chronic, debilitating, hereditary blood disorder with an occurrence in 1 in 500 African Americans. SCD results from a point mutation in the β-globin gene, resulting in abnormal expression of hemoglobin S (Hb S).[1] In the presence of deoxygenation, Hb S polymerizes within red blood cells, leading to erythrocyte rigidity and membrane damage.[2] Homozygous Hb SS ($\alpha_2\beta_2^S$), with two copies of abnormal β-globin chain, is associated with anemia, repeated ischemia-reperfusion injury, and inflammation affecting ultimately all organ systems leading to acute chest syndrome, stroke, widespread vasculopathy, and kidney disease.[3,4] Overall, SCD is a chronic condition that is vulnerable to vascular injury.

Grant Support: Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number P20GM109021. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Young Investigator Grant of the National Kidney Foundation and Grant number U54-GM104941 (PI: Binder-Macleod) funded the project, in part. The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: None.

Clinical Trial Registration: Not applicable.

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1933-1711/$ - see front matter
https://doi.org/10.1016/j.jash.2018.04.005

Reports on the prevalence of hypertension in SCD have been conflicting. Despite intermittent episodes of pulmonary hypertension, early reports described low systemic blood pressure (BP) and a low prevalence of systemic hypertension in individuals with SCD compared with healthy controls.[5–8] These reports were largely based on BP recordings obtained during hospitalization or clinic visits in adults with SCD. A more recent report described a quite different observation on BP levels in adult SCD patients. Gordeuk et al. examined BP levels as well as renal and cardiac status in 163 SCD adults, with a second evaluation 2 years after the baseline measurements in 86 patients. In the entire SCD cohort, 44% met criteria for prehypertension and 10% met criteria for hypertension.[9] Moreover, SCD patients with prehypertension and hypertension were at greater risk for pulmonary hypertension and renal dysfunction. Children and adults with SCD and elevated BP are at increased risk for silent cerebral infarcts, and stroke,[10,11] thus highlighting the importance of early recognition and management of BP abnormalities in youth with SCD. Ambulatory BP monitoring (ABPM) is the most appropriate BP measurement method that eliminates white coat effect and allows assessment of nocturnal BP.[12] There are very limited studies that used 24-hour ABPM to examine BP levels and patterns in children with SCD. The purpose of this study is to describe the prevalence of abnormal BP patterns in a cohort of children with SCD. All SCD participants had Hb SS or Hb Sβ^0 thalassemia, the most severe genotypes of SCD.

Patients and Methods

Study Setting and Study Design

We used a cross-sectional study design to investigate early markers of nephropathy including BP assessment in pediatric SCD. At enrollment, participants were clinically stable with regular attendance at the Sickle Cell Center at Nemours/A. I. duPont Hospital for Children, Wilmington, DE; Nemours Children's Hospital, Orlando, FL; and Nemours Children's Clinics, Pensacola, FL.

Participants

Participants were enrolled if they had hemoglobin electrophoresis-confirmed diagnosis of SCD (Hb SS or Hb Sβ^0 thalassemia), and were between the ages of 5 and 20 years at the time of enrollment. History of bone marrow transplant was an exclusion criterion. The protocol was approved by the Institutional Review Board at Nemours for protection of subjects, and adhered to all standards set forth by the Declaration of Helsinki. The parents of each participant younger than 18 years of age provided written informed consent, and each child above the age of 7 years provided assent, before enrollment in the study. Written informed consents were obtained by participants 18 years of age or older.

Study Procedures

Information about prior history of SCD-related complications was collected—including episodes of vaso-occlusive pain crises, acute chest syndrome, stroke, splenic sequestration, and number of hospitalizations and emergency room visits. Current need for chronic blood transfusion, and hydroxyurea therapy were recorded by completing interviews with patients and families and by reviewing the patient's electronic medical records. All evaluations were conducted in an outpatient setting in coordination with participant's routine hematology clinic visits. Blood samples for this study were obtained at the same time as participant's routine clinic blood investigations, to prevent additional phlebotomy.

Baseline characteristics obtained on each participant included age, gender, weight, height, body mass index (BMI) percentile, BMI Z-score, and clinic BP. Clinic BP on each participant was obtained in the seated position using a BP cuff that was appropriate for arm size. BP measurements were obtained with an oscillometric device (GE CARESCAPE V100). A random blood sample was used for hemoglobin and hematocrit. Serum creatinine and cystatin C were obtained to assess estimated glomerular filtration rate (eGFR) with age-based formulas. A spot urine sample was used to estimate urine sodium, potassium, osmolality, albumin, and creatinine.

Twenty-Four–Hour ABPM

To obtain in-depth BP data, we obtained 24-hour ABPM studies in our SCD participants using the Spacelabs 90,217 or 90,227 ambulatory monitors (Spacelabs Medical, Issaquah, WA, USA), monitors validated in pediatric patients. Participants underwent ABPM only if they were pain-free during the BP monitoring period and were at least 4 weeks from their last pain crisis or acute chest syndrome or any other recent emergency room visit or hospitalization.

ABPM was performed by a trained nurse practitioner. An appropriate-sized cuff was attached to the nondominant arm, and the device was programmed to record BP every 30 minutes during sleep and every 20 minutes during awake hours. Participants were instructed to resume their normal activities while wearing the monitor, but requested to avoid strenuous activities including sports. Each participant (or parent) recorded medication administration, activity, and sleep and awake times during the study. ABPM parameters included mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) during the entire 24-hour, awake, and sleep periods; BP load (percentage of readings above the ambulatory 95th percentile) for both SBP and DBP during the entire 24-hour, awake, and sleep periods; and dipping that refers to the physiologic decline in SBP and DBP during sleep.[12] Normal dipping is defined as a $>$10% decline in mean ambulatory SBP and DBP levels from awake to sleep period. ABPM measures were