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Original Article

Reliability and Clinical Correlation of Transcranial Doppler Ultrasound in Sturge-Weber Syndrome

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ABSTRACT

BACKGROUND: The reproducibility of transcranial Doppler (TCD) ultrasound measurements in Sturge-Weber syndrome (SWS) and TCD's ability to predict neurological progression is unknown. **METHODS:** In 14 individuals with SWS, TCD measured mean flow velocity, pulsatility index, peak systolic velocity, and end-diastolic velocity in the middle, posterior, and anterior cerebral arteries of the affected and unaffected hemisphere. TCD was performed either once (n = 5) or twice in one day (n = 9). We assessed the reproducibility of the measurements performed twice on the same day on subjects and compared the TCD measurements to previously published age-matched controls. Clinically obtained neuroimaging was scored for extent and severity of SWS brain involvement. Patients were prospectively assigned SWS neuroscores. **RESULTS:** Middle cerebral artery velocity ($r = 0.79$, $P = 0.04$, n = 7), posterior cerebral artery velocity ($r = 0.90$, $P = 0.04$, n = 5), and anterior cerebral artery pulsatility index ($r = 0.82$, $P = 0.02$, n = 7) were reproducible TCD measurements comparing same-day percent side-to-side differences. In subjects with SWS, affected and unaffected mean peak systolic velocity and end-diastolic velocity in the middle, posterior, and anterior cerebral arteries were globally lower compared with age-matched control subjects. Subjects with the lowest affected middle cerebral artery velocity had the greatest worsening in the total neurological score between time 1 and 2 ($r = -0.73$, $P = 0.04$, n = 8) and the most severe magnetic resonance imaging involvement of the affected frontal lobe ($r = -0.82$, $P = 0.007$, n = 9). **CONCLUSIONS:** TCD may be a reliable measure with potential clinical value, indicating that blood flow may be globally decreased in SWS patients with unilateral brain involvement.

Keywords: transcranial Doppler ultrasound, Sturge-Weber syndrome, peak systolic velocity, end-diastolic velocity

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Introduction

Sturge-Weber syndrome (SWS) is a neurocutaneous syndrome consisting of leptomeningeal angioma of the brain, a facial capillary malformation (port-wine birthmark), and capillary venous malformation of the eye.[1] SWS is caused by an R183Q somatic mutation in *GNAQ* occurring during fetal development.[2,3] Individuals with SWS often experience seizures and stroke-like episodes.[1] The extent of brain involvement is formally assessed using magnetic resonance imaging (MRI) of the brain with and without intravenous contrast. The contrast specifically highlights the stereotypical leptomeningeal angiomatosis enhancement in affected individuals. However, low sensitivity of neuroimaging in infancy makes it challenging to confirm early SWS brain involvement. Furthermore, MRIs of the brain at this point frequently require conscious sedation and intravenous contrast administration, hindering the accessibility of the MRI as a biomarker for monitoring patient response to treatment. Early suspicion of brain involvement can be assessed using electroencephalographs, although in some instances the electroencephalograph and subsequent MRI are not concordant or may not correlate with neurological symptoms.[4] The SWS community is in need of an additional, early detection tool to screen for SWS brain involvement and a noninvasive biomarker to evaluate treatment response.

Research has demonstrated that individuals with SWS brain involvement have decreased cerebral blood flow in involved regions of the brain.[5,6] Transcranial Doppler (TCD) ultrasound is a noninvasive vascular procedure that measures velocity of blood flow throughout the brain's blood vessels. TCD has been used successfully in individuals with neurovascular disorders (specifically stroke prevention in sickle cell disease) to predict neurological progression.[7] To test the utility of TCD in assessing cerebral blood flow in patients with SWS brain involvement, Jordan et al.[8] evaluated eight children with unilateral brain involvement by TCD performed once to assess non–angle-corrected mean flow values (centimeters/second) for the velocity, depth, and pulsatility index (PI). Those with SWS had lower middle cerebral artery (MCA) velocity and posterior cerebral artery (PCA) velocity TCD and higher MCA PI values on the affected hemisphere compared with the unaffected hemisphere. It is therefore concluded that TCD was a promising tool for monitoring abnormal blood flow in SWS. A larger number of subjects were needed to seek correlations with neurological status and additional comparisons with age-matched control subjects were also required. Therefore the goals of this study are threefold: (1) assess reproducibility of TCD ultrasound measurements in subjects with SWS; (2) determine whether there is an association in changes in TCD with clinical change; and (3) compare TCD results with age-matched normal subjects.

Methods

The Johns Hopkins Institutional Review Board approved this study and the subjects or their legal guardian signed informed consent for their participation.

Participants with a diagnosis of SWS unilateral brain involvement as defined on neuroimaging were eligible for this study. Participants were recruited from the Kennedy Krieger Institute (Baltimore, MD) as patients of A.M.C and came from Maryland and the neighboring states. Participants were recruited prospectively. No subjects were excluded. Age-matched control data for mean flow velocity, peak systolic velocity (PSV), and end-diastolic velocity (EDV) were obtained from Bode and Wais.[9]

TCD was performed by a clinical ultrasonographer, M.R.D., on an ATL/Philips Model 5000 (Bothell, WA) and a Siemens Antares (Malvern, PA) for the participants who received TCD once ($n = 5$) and on an ATL/Philips Model 5000 and a Philips IU-22 for the participants who received TCD twice in 1 day ($n = 9$). No repeat TCD data are available for the participants reported in the study by Jordan et al.[8] Standard clinical procedures were used with three different clinical models that supported TCD to avoid participants waiting for the unit to be available; all models had preventative maintenance every 6 months. Using previously described methods, the non–angle-corrected mean, PSV and EDV (centimeters/second), and the PI were measured for the MCA, PCA, and anterior cerebral artery (ACA) using a 2-MHz probe during approximately 90-minute sessions.[8] Not all TCD measurements were able to be collected for each participant because of subject cooperation (see Supplemental Table 1 for details). For participants with multiple velocities, the highest velocity per session for each hemisphere of each TCD vessel was used in the analyses. TCD measurements were done without being aware of both MRI scores and SWS clinical severity scores.

Average differences and average percent side-to-side differences (PSSDs) of TCD values were calculated to compare the first TCD session to the second. Reproducibility of the TCD measures was evaluated using Spearman's correlation with two measurements done on the same day on the same subjects ($n = 9$). For the participants that had more than one session, the average TCD value for the sessions was calculated for each hemisphere; similarly, an average percent difference between the affected and unaffected hemisphere was calculated for the two sessions.

SWS clinical severity scores were collected prospectively (A.M.C.), on average, at the time of the TCD and 12 months later. Differences were calculated for each subcategory of the clinical severity scores between the two assessment dates. An SWS clinical severity score contained frequency of seizures, severity of hemiparesis, assessment of visual field cut, degree of cognitive functioning with a total score ranging from 0 to 15 as previously published (see Supplemental Table 2).[10] Correlations of TCD values with the SWS clinical severity scores were evaluated using Spearman's rho. TCD values of those with two sessions were averaged together. PSSDs of TCD values were calculated between the affected and unaffected side of the brain as follows:

$$\left(\frac{(\text{Affected TCD value} - \text{unaffected TCD value})}{\text{affected TCD value}}\right) \times 100$$

MCA, PCA, and ACA velocities were compared between affected hemispheres and unaffected hemispheres and also compared with previously published age-matched normal values using Wilcoxon matched-pairs signed rank tests.[9] For brevity, only significant results have been reported.

All subjects had prior brain MRI with and without contrast imaging done for clinical reasons. The time between MRIs and the date of TCD ranged from 7 months to 10 years and 6 months with a median time range of 1 year and 3 months. Each MRI was rated by D.D.M.L and A.M.C., who were not aware of the TCD and clinical severity scores. The raters scored MRI scans individually and then came to consensus on discrepancies. A Likert scale of 1 to 4 (1 = "no asymmetry," 2 = "mild asymmetry" [atrophy or angiomatosis only], 3 = "moderate asymmetry" [angiomatosis and mild atrophy], and 4 = "severe asymmetry" [angiomatosis and severe atrophy]) was used to assign a score for the frontal, parietal, occipital, and temporal lobes of the brain in both hemispheres (adapted from Jansen et al.[11]). Correlations of MRI severity scores with TCD values and clinical severity scores were evaluated using Spearman's rho.

Nonparametric analyses were used for correlations because of the noncontinuous and semiquantitative nature of the scales and/or nonnormal and small data sets. Inter-rater reliability was evaluated using Cohen's weighted kappa (κ_w). *P* values less than 0.05 for two-tailed analyses were used as the threshold for determining significance. All analyses were conducted using IBM SPSS Statistics 23.0 and 24.0 software.