

The Use of Transcranial Echo-Doppler Ultrasonography to Predict Stroke in Patients with Sickle Cell Disease

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Received: February 18, 2019; **Published:** March 22, 2019

Abstract

Stroke is a severe clinical disorder and with a high incidence in sickle cell disease. Studies demonstrate that primary prevention using blood transfusing therapy is reliable and using Transcranial echo-Doppler, which allows to assess flow velocities of intracranial arteries, it's possible to determine the risk of stroke in patients with this disease.

Keywords: Sickle-Cell Disease; Stroke; Transcranial Echo-Doppler

Abbreviations

SCD: Sickle-cell Disease; SCA: Sickle-cell Anemia; Hb: Hemoglobin; HbS: Sickle Hemoglobin; TCD: Transcranial Echo-Doppler; TMM: Time-average Maximum Mean Velocity; PSV: Peak Systolic Velocity; ICA: Internal Carotid Artery; ACA: Anterior Cerebral Artery; MCA: Middle Cerebral Artery

Sickle-cell disease

Sickle-cell disease (SCD) or sickle-cell anemia (SCA) is an inherited, anaerobic severe disease, associated with an elevated risk of pneumococcal infection and stroke, which results in early death and morbidities. It's more commonly found in children and afro-descendant individuals and the report of new cases has increased over the past few years [1,2]. SCD results from a specific abnormality in the hemoglobin (Hb) molecule: glutamic acid is replaced for valine at the 6-position of the β chain. As a result, HbS is produced instead of HbA and this mutation can be expressed in diferente genotypes: homozygous HbSS or heterozygotes such as HbSC or HbS- β (β -thalassemia) [3]. Sickle hemoglobin (HbS) polymerizes on deoxygenation, metabolic acidosis or dehydration, changing the structure of the red blood cells by making them rigid and sickle-shaped which dificults the transport of oxygen and increase their prone to hemolysis [4-7]. Patients have choric hemolytic anemia and severe vaso-occlusive crises leading to pain and irreversible cardiovascular damages [8].

Stroke

Stroke represents the most significant threat to individuals with SCD. Studies demonstrate that the onset of cerebrovascular changes begins in children between the ages of 2 and 5 and the highest incidence rate of stroke is 11% ate the age of 20 [9-11]. This incidence rate appears to be influenced by the HbS genotype, being more severe in HbSS, following HbSC and lower for HbS- β [5,7,12].

In addition to the mechanisms above, endothelial dysfunction, hypercoagulability and disturbance in nitric oxide metabolism increases the blood flow velocity, which explains the higher risk of stroke and brain injury in this disease [4,8,13,14].

Transcranial echo-Doppler and primary prevention

Transcranial echo-Doppler (TCD) is a noninvasive technique that allows to measure in real time blood flow velocity in the large intracranial arteries of the circle of Willis. So currently it's a very useful tool to primary prevention of stroke by monitor the cerebrovascular disease in individuals with SCD, since these lesions can progress for many years without any symptoms. Besides that, it is an inexpensive, portable and non-invasive method, being safe, painless and more tolerable for the children [3,4,13,15].

Based on increased blood flow velocity, to make up the hyperemia due to the chronic anemia that limits the oxygen supply in SCD, TCD can stratify the risk of stroke which is classified according to the velocities obtained [16]. These can be determined by monitor time-average maximum mean velocity (TAMM) and by peak systolic velocity (PSV) criteria in the distal intracranial internal carotid artery (ICA), anterior cerebral artery (ACA) and middle cerebral artery (MCA). Based on TAMM, values ≥ 200 cm/s are considered of a high risk of 40%, between 170 - 199 cm/s a conditional speed and therefore an intermediate risk of 7%, and < 170 cm/s for a low risk with 2% of occurrence [8,13,14,17].

These values differ for children due to physiological differences such as lower vessel size, decreased hematocrit and cerebral metabolism so flow velocities above 220 cm/s are considered a high risk [18,19].

The pick systolic criteria is based on different reference values: > 250 cm/s represents a high risk, 200 - 249 cm/s an intermediate and < 200 cm/s a low risk of stroke [16].

In addition to the increased velocities there are some other representative signs of stroke in SCD such as silent infarcts diagnosed by Magnetic Resonance, transient ischaemic attack and intracranial stenoses [20]. MoyaMoya syndrome may also be associated with SCD, so in this cases flow velocities below 70 cm/s in the Willis circle should be assumed as a risk for hemorrhagic stroke [10,14,15,21].

In 2014 the National Heart, Lung and Blood Institute (NHLBI) published the American guidelines for SCD, recommended annual TCD screening for primary prevention from 2 to 16 years of age [22]. According to the Stroke Prevention Trial in Sickle Cell Anemia (STOP), after this evaluation there are protocols to be taken depending on the risk determined. For conditioned flow velocities, screening is indicated every 3 months and for high-risk patients every 2 weeks with blood transfusions at intervals of 3 to 4 weeks to avoid events [19].

Adams, *et al.* [16] proved the risk of stroke decreased about 90% in patients undergoing prophylactic red blood cell transfusion in order to maintain the Hb genotype $< 30\%$ [17,21,23].

However blood transfusions are costly and toxic to the organism, so in this way Switch Trial comes up as an alternative form of treatment using Hydroxyurea, which induces the production of fetal Hb and normal red blood cells [24,25]. These two treatments are currently used allied [12,26].

Barriers and strategies

Although the STOP protocol has demonstrated to be an effective stroke prevention guide, evidence suggests that delivery of these interventions is suboptimal and TCD screening rates continue to be low. Studies have identified several barriers that limit the whole process such as not being informed and aware of the disease and its consequences, lower levels of social support and living at a long distance from the medical centers [27]. Thus identification of new interventions to reduce missed opportunities for TCD screening and implementation of system improvements based on access to specialty care and family education could decrease the adverse outcomes associated with SCD [28].

Some strategies go through inform caregivers about the stroke risk, aware physicians to the TCD screening guidelines, offer screening at the same time as clinic appointments [29]. To medical barriers associated with long travel distance there are other ways such as community health workers, developing telemedicine and mobile health centers, emerging satellite clinics. The purpose of these clinics is to

provide all medical care as the medical center, from TCD screening to give hydroxyurea therapy, as well as providing SCD education to patients and family [30].

Future researches

Future researches are intended to relate other DTC markers with the risk of stroke such as evaluation of flow velocities in cerebral posterior circulation, turbulence an inverted flow and correlate this data with other diagnostic tests including Angiography, Magnetic Resonance Imaging and Computed Tomography [18,19]. Besides that, other future researches are needed to document the successful use of care guidelines in order to sustain such strategy as satellite clinics [30].

Conclusion

Transcranial echo-Doppler can determine patients at a high risk of stroke and should be use as primary prevention measure to classify this risk according to the STOP trial. The National Heart, Lung and Blood Institute guidelines strongly recommend children with SCD to receive na anual TCD screening. Developing a plan to assess and screen all SCD patients is crucial to improve health outcomes and reduce the incidence of pediatric stroke.

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Volume 6 Issue 4 April 2019

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