Scientific Research Publishing

Neuroscience & Medicine, 2019, 10, 162-173
http://www.scirp.org/journal/nm
ISSN Online: 2158-2947
ISSN Print: 2158-2912

Transcranial Doppler Ultrasonography to Prevent Cerebrovascular Accident in Children with Sickle-Cell Disease

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How to cite this paper: Carpentieri-Pipolo, G., de Lima Oliveira, M., Paschoal Junior, F.M. and Bor-Seng-Shu, E. (2019) Transcranial Doppler Ultrasonography to Prevent Cerebrovascular Accident in Children with Sickle-Cell Disease. *Neuroscience & Medicine*, **10**, 162-173.
https://doi.org/10.4236/nm.2019.102011

Received: March 12, 2019
Accepted: June 7, 2019
Published: June 10, 2019

Abstract

Sickle-cell disease (SCD) is the most common cause of ischemic stroke in children and it happens in about 11% of patients between the age of 2 and 20 years old. About 7% of the world population is affected by hemoglobin disorders, mostly sickle cell anemia. SCD has a high prevalence in the population of African offspring and it is a public health problem in Brazil that affects more than 30,000 million people. Prevention of primary stroke might be feasible with a way to identify children at greatest risk. Transcranial Doppler Ultrasonography (TCD) to SCD patients can be a valuable service that results in a significant decrease of first stroke rates. In this work, we present a review about TCD as an effective strategy to detect children with SCD who are at risk for stroke.

Keywords

Transcranial Doppler, Sickle Cell Disease, Stroke in Children, Cerebrovascular Disease

1. Introduction

Sickle-cell disease (SCD) is considered to be the most common inherited hematological disease in humanity; and was recognized as a hemoglobinopathy disease in Africa several hundred years ago; and it has been less than a century since the initial observation of the abnormal morphology of red blood cells (reported by Linus Pauling, 1949) that defines the disorder [1]. It is an autosomal recessive genetic condition resulting from deformity in hemoglobin (Hb) associated or

not with deformity in its synthesis. The molecular misprint—substitution of a valine for glutamic acid in the sixth position of the α globin chain—was identified by 1957 [2].

It is characterized by the presence of the S hemoglobin (HbS), originated by a mutation on the 11th chromosome in the S-beta globin gene, a normal codon (GAG) is replaced by another (GTG), thus resulting in exchanging the sixth amino acid of the beta globin that leads to the replacement of glutamic acid by valine in the sixth position of the β globin chain ($\beta^{6\ GLU\rightarrow VAL}$). The replacement of a single amino acid changes hemoglobin S format from round shape to form of sickle [3] [4] [5] [6].

The sickle shape of red blood cells is responsible for the whole pathophysiology. Normal red blood cells can live up to 120 days. But, sickle cells only live for about 10 to 20 days. Also, sickle cells may be destroyed by the spleen because of their shape and stiffness. The spleen helps filter the blood of infections. Sickled cells get stuck in this filter and die. With less healthy red blood cells circulating in the body, patients can become chronically anemic. The sickled cells also damage the spleen thus SCD patients are at greater risk for infections [7] [8] [9].

One of the devastating complications of SCD is stroke, because of its high morbidity-mortality. In fact, SCD is the most common cause of ischemic stroke in children. It happens in about 11% of patients between the age of 2 and 20 years old [8] [10].

Although there are several predictors of probability of an asymptomatic child with SCD to have a cerebral infarction, including history of transient ischemic attack, acute chest syndrome within the previous 2 weeks, annual rate of acute chest syndrome, degree of anemia, raised systolic blood pressure however, none of them can predict stroke without the evidence of a previous symptomatic event [6] [11].

Transcranial Doppler Ultrasonography (TCD) is a more effective, harmless and non-invasive test, which allows dynamic monitoring of cerebral circulation by measuring the blood flow velocity from the Willis polygon arteries and from the measurement is possible to establish the ideal blood flow velocity for patients with sickle cell anemia, and most importantly, which blood flow velocity represents risk of cerebral infarction (meaning overt stroke or silent infarction) [7] [8] [10] [12] [13].

In this review we summarize the current knowledge on the role and the importance of the use of Transcranial Doppler Ultrasonography (TCD) as a tracker in primary prevention of stroke in children with sickle cell anemia.

2. Methods

The studies for this review were obtained through exhaustive online computer searches for articles on topics thought to be important and aligned to the main subject of the research.

The following databases were utilized: MEDLINE, PubMed, Scopus, Cochrane Library, SciELo and Web of Science. The following key words were used: Transcranial Doppler, Sickle cell disease, stroke in children, Cerebrovascular disease (**Figure 1**).

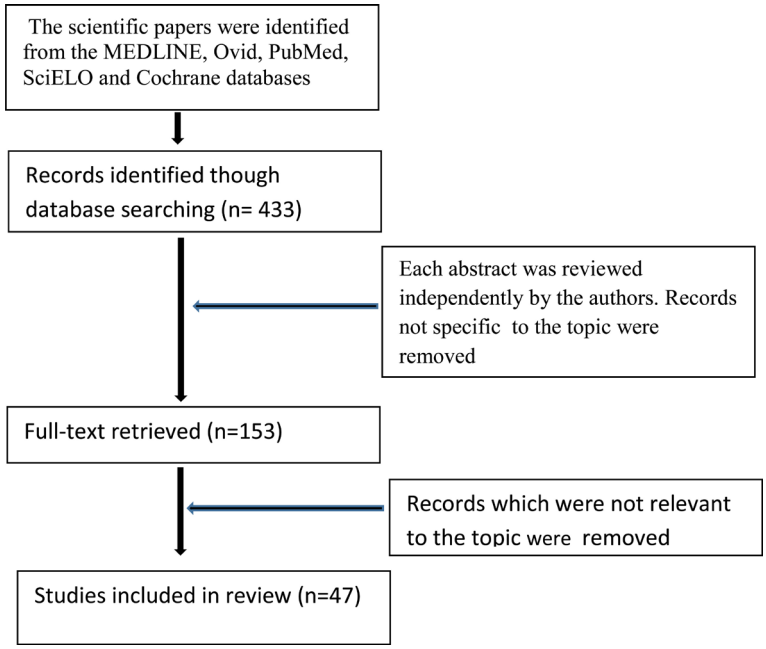

Figure 1. Process of literature selection.

3. Results

3.1. Etiology, Epidemiology and Risk Factors

Hemoglobinopathies resulting from structural mutations are more prevalent in people with African offspring and thalassemias due to deformities in Hb synthesis in Mediterranean, Asian and Chinese peoples. Despite this ethnic preference, SCD is present on all continents, as a consequence of population migrations. According to World Health Organization (WHO), the World Bank and the Ghana Sickle Cells Foundation, 500,000 children are born in Africa each year with SCD, however, with migration and miscegenation, sickle cell anemia is considered to be a public health problem in Brazil, in the United States, and in African countries [14] [15] [16]. Sickle cell disease affects over 70,000 individuals in the United States, and there are at least 75,000 hospitalizations costing over $500 million annually for treatment of SCD complications [17] [18] [19].

About more than 7 million people are carriers of HbS, in Brazil, of which approximately 25 to 30 thousand have the homozygous form, with more than 3500 new cases emerging each year [20] [21].

In Brazil, which is one of the world most genetically heterogeneous populations, the highest prevalence of the disease occurs in the North and Northeast Regions. It has been estimated that more than seven million people have hemoglobin S in Brazil, and that more than 25,000 to 30,000 people have the homozygote form, with more than 3500 new cases born every year it is prevalent in states where are the highest concentration of African offspring population [18]. It was introduced in Brazil by the slave trade during the colonial period, mainly in the Northeast for working sugarcane plantations and, and later in the state of Minas Gerais, to extract precious metals. Bahia state is the Brazilian state with

the highest incidence of the disease (5.3%) with about 1 case per 650 live births, 4% in Pernambuco (1:1400 live births), 4% in Rio de Janeiro (1:1200 live births), 3% in Minas Gerais (1:1400 live births), 2.4% of the population of São Paulo (1:4000 live births), and occurring in 2% in Rio Grande do Sul (1:10,000 live births) [17] [18] [19].

The determinant mutation of the HbS gene is due to the substitution of a nitrogenous base, adenine (A), and thymine (T), in the sixth codon of the beta gene. This causes polymerization of hemoglobin S makes the erythrocytes which contain the S hemoglobin, in hypoxia conditions, to take the shape of a sickle, causes low oxygen tension which leads to sickling of red blood cells, due to the polymerization of the hemoglobin, and in that shape, the erythrocytes are not capable of circulating properly through the blood microcirculation, what can originate microvascular vaso-occlusion, and premature destruction of red blood cells (RBC). This vaso-occlusive process is responsible for most of the clinical manifestations of sickle cell disease. The early identification of patients before the symptoms starts aims to reduce the vasoconstriction episodes, also called sickle cell crises. The crises, are caracterized by strong pain, ischemic tissue damage and injury on all organs and systems (brain, heart, liver, kidneys, skin, eyes, skeleton and lungs) [9] [22].

It is known that sickled erythrocytes are adherent to the vascular endothelium; whereas regular RBC are detached Hebbel *et al.*, 1980. The consequences of this adherence is the trapping of denser less deformable cells, which prolongs transit time and enables polymerization of sickle hemoglobin, resulting in vaso occlusion. In addition, the adhesion of the sickle cell leads to a series of events that inhibits vasorelaxation and increase the surface expression of additional adhesion molecules, generating architectural remodeling of the vessel wall and vasculopathy [23].

The incidence of stroke in children with SCD from age group 2 to 5 years old is 1.02%, this is high compared to the percentage of the overall incidence of stroke in the pediatric population: about 0.00129%, assuring that the child with sickle cell anemia is 280 times more susceptible of having a stroke [24] [25].

According with Cooperative Study of Sickle Cell Disease (CSSCD), a multi-institutional investigation research study (USA), which involves data collection of 23 institutions on 3800 patients from birth through adulthood called observed that the median survival of men and women with SCD was 42 and 48 years, respectively. They also observed that stroke is one of the main causes of morbidity and mortality, with an incidence of 0.61 events per 100 patient-years by CSSCD (Cooperative Study of Sickle Cell Disease). It mainly affects children (19), with an incidence of 11% in individuals under 20 years old being predominant in children under 10 years old, with a rate of 1.02 per 100 patient-years in those with 2 And 5 years old and a rate of 0.79 per 100 patient-years in children with 6 to 10 years old. Ischemic AVEs are more prevalent in young patients younger than the ones with 20 years old, whereas in older patients with hemorr-

hagic stroke is most common [24].

According to the Cooperative Study for Sickle Cell Disease (CSSCD), United States (USA), demonstrated that 17% of patients with SCD and no previous story of clinical cerebral infarction have cerebral lesions compatible with cerebral infarction or ischemia. In addition, patients older than six years old, the prevalence of these silent lesions has a discrete increase, suggesting progressive cerebral lesion [26] [27] [28].

Cerebral infarctions generally occur due to a large arterial vasculopathy which narrows and occludes the brain microvasculature, involving intracranial supplier arteries, leading to deprivation of blood to the brain. Stenotic lesions involve primarily large vessels in the intracranial internal carotid, middle, and anterior cerebral circulation and can progress for months and years before symptoms develops [3].

Silent infarctions are the most common cause of neurological impairment in sickle cell anemia. Differently from clinically evident stroke, it is associated with cerebral vasculopathy of large and medium-sized vessels, silent infarctions do not involve large arteries. These lesions are typically small (85% are ≤2.5 cm) and are mainly distributed in the white matter of the frontal and parietal lobes. The basal ganglia or thalamus, and brainstem or cerebellum, are less involved. Silent infarctions occur in 37% of children before 14 years old and are associated with lower baseline hemoglobin, high systolic blood pressure and male sex [13] [24].

The cerebrovascular event can bring severe sequela in 7% of children with sickle cell anemia, with the possibility of new episodes (0.7% per year) during the first 20 years of life. The episodes could happen isolated or associated with other symptoms as well as infection, dehydration, acute painful crises, aplastic crises, priapism, among others [10].

3.2. Diagnostic Imaging Methods TCD

The use of transcranial Doppler (TCD) was realized at the first time in the 1990s by through the STOP (Stroke Prevention Trial in Sickle Cell Anemia) to identify patients with higher risk of the stroke. STOP has performed several studies and a large clinical trial (more than 2000 sickle cell children) to validate STOP using transcranial Doppler among individuals with sickle cell anemia to demonstrate the usefulness of this examination for evaluating stroke risk [7] [8] [9].

The STOP study have shown that children with sickle cell anemia from 2 to 16 years' old whom had the increased risk of cerebral infarction, with regular transfusion regimen, the occurrence of stroke was reduced from 10% per year to less than 1% per year. Also, the risk of recurrence of a new acute brain event was reduced 92% [29] [30] [31] [32].

The positive attributes that explain why in recent years the applications for TCD have grown and it is widely accepted as the modality of choice for screening intracranial vessels in children with sickle cell disease are that it is noninvasive (no need for sedation, contrast material, or radiation), portable, easily repeated, and it provides information about the intracranial vessels that is other-

wise unavailable. Doppler (TCD) is the most cost-effective method of screening for stroke risk in children with sickle cell disease. TCD is used to identify areas of stenosis by increased flow velocities across the narrowed segments of vessel, this is possible because blood flow velocity is directly related to the diameter of the artery: the more occluded and narrowed the vessel is, its blood flow velocity will be higher. Risk of stroke rises with velocity such that for each 10 cm/sec rise above the median velocity, there is a 39% increase in stroke risk [28] [33]-[39].

TCD allows the early detection of arterial abnormalities in individuals with sickle cell anemia, since the brain lesions appear to progress for months or years before the onset of symptoms The test measures the velocity of blood flow in the intracranial vessels of the circle of Willis, which is influenced by several factors, of which the three main factors are: the difference in gradient pressure along the vessel, vessel length and cross-sectional area (caliber), and the blood viscosity [7].

The test may detect changes in cerebral blood flow, which is identified by the increased of blood flow velocity as a result of reduced arterial diameter. In sickle cell anemia, there is an increase of cerebral blood flow speed due to severe anemia. The high blood flow velocity when measured by TCD is a powerful predictor of stroke, which the risk increases in the direct proportion with the increase of the time-averaged of the maximum velocity—TAMMX (21). TAMMX was used in the development of the STOP TCD velocity criteria [7] [31].

Time-averaged mean of the maximum velocity refers to the time mean of the peak velocity envelope, the envelope being a trace of the peak flow velocity as a function of time. Traditionally, systolic, diastolic, and mean values are used to describe pressure, flow, and velocity in the arterial system. It means carries the highest physiological significance because it depends less on central cardiovascular factors such as heart rate, contractility, total peripheral resistance, and aortic compliance than do systolic or diastolic values. Moreover, the TAMMX correlates better with perfusion than peak and trough values [7] [31] [32].

TCD is a non-invasive method, relatively inexpensive, and well tolerated in children. The principle for the association between cerebral vasculopathy, stroke increases vascular encephalic accident (AVE), and cerebral blood velocity is based on physical principles, which state that the flow velocity increases occurs when there is a decrease in the cross-sectional area. In addition, there is a decrease in the pressure in the distal region of the vessel which is particularly occluded [11].

According to the STOP TCD results were classified to indicate degree of risk for stroke as normal, conditional, abnormal, or inadequate. The STOP trial defined values for blood flow velocity: up to 170 cm/s (normal); from 170 to 200 cm/s (conditional); and greater than 200 cm/s (critical/abnormal), with a high risk of developing stroke in children with 2 to 16 years old [7]. Adams *et al* (1998) using TCD, in non-asymptomatic patients, have shown that patients with sickle cell anemia have a cerebral blood flow with a time-averaged mean of the maximum velocity—TAMMX (labeled TAP with ATL/Philips, TAMMX with Acuson) in the MCA > 170 cm/s was an indicator of a patient at risk for development of stroke, thus 40% - 50% higher in the large vessels of the Willis poly-

gon than of the healthy controls. A child with a low stroke risk typically has a TAMMX of 130 cm/s and a PSV of 200 cm/s. A TAMMX of 200 cm/s or PSV of 250 cm/s is abnormal. They also have found that children with SCD who had cerebral flow velocity above the 95th percentile had a higher risk for stroke (AVE). Very often the normal cerebral blood flow of these patients is associated with vessel stenosis. The purpose of the TCD examination is to identify the highest TAMMX velocities. This requires careful tracking of the entire vessel with optimization of the wave form. Time-averaged mean of the maximum velocity refers to the time mean of the peak velocity envelope, the envelope being a trace of the peak flow velocity as a function of time [7] [26] [28] [29] [33] [34] [35] [36].

The time required for the Transcranial Doppler examination to be repeated will depend on the result obtained. If the initial TCD is normal (TAMMX < 170 cm/s), follow-up should be performed annually; If conditional is low (TAMMX 170 - 184 cm/s), every 6 months; If conditional is high (TAMMX 185 - 199 cm/s), every 3 months; and if it is abnormal the follow-up should be performed within 1 month (TAMMX ≥ 200 cm/s) [32]. Children whose mean velocity time in the distal portion of the internal carotid artery or middle cerebral artery is abnormal have approximately six times greater risk of stroke than those with normal velocities (<170 cm/s), reaching a 9% risk per stroke per year. Stroke may also occur in patients with conditional velocities (TAMMX between 170 and 199 cm/s), with an estimated risk of 2% - 5% per year [28] [37].

The relationship between high measures of TCD and the incidence of stroke appears to be dependent of age. Individuals over 16 years old do not appear to have a significant increase in the risk of stroke with elevated TCD measurements, but studies are still needed to demonstrate if there is association with this disorder (14). There is no consensus regarding the management of children with conditional velocities. Although conditional velocities can normalize or remain conditional, a substantial proportion of patients will convert to abnormal values. In the STOP study the conversion rate to abnormal TAMMX values was approximately 29% among children with at least one conditional velocity and 55% among children with two tests with conditional values TAMMX 185 - 199 cm/s [32].

Although not all strokes can be prevented by transfusion therapy, repeated TCD studies would probably identify the minority of individuals who convert from normal to high risk. The risk of recurrent stroke on a periodic transfusion regimen could be as low as 13% a significant reduction when compared with the natural history of close to 70% [4] [7] [12].

Based on the STOP study, the United States National Heart, Lung, and Blood Institute (NHLBI) recommended that children with SCD between 2 and 16 years should be screened for TCD every 6 months, and that those identified as having a high risk of stroke should receive regular transfusion for prevention [40] [41] [42] [43] [44].

The STOP II study identified 79 children with normal magnetic resonance SCD and altered TCD who, when receiving regular transfusion therapy, normalized speed of cerebral blood flow (CBFV). Part of these patients, 38 children with

SCD, received regular transfusion and part received no transfusion (41 children). After approximately 30 months of follow-up, 14 of the 41 non-transfused children again had TCD changes with a high risk of stroke and two children had a stroke. In the group of children undergoing transfusion, no child had an acute brain event. This study was stopped two years earlier and demonstrated that transfusion treatment in children with SCD and changes in TCD should not be discontinued otherwise the patients return to an increased risk of stroke. In addition, it has been shown that transfusion suspension is also associated with the development of silent cerebral infarction [13] [26].

Recently, with the intention of expanding health policies for SCD, and to contribute in reducing morbidity and mortality resulting from this pathology, was developed the Brazilian guidelines on the use of transcranial Doppler in sickle cell disease patients. This work was developed in line with the National Newborn Screening Program which guarantees universal access of newborns to screening for hemoglobinopathies which establishes guidelines for the National Policy of Comprehensive Care for People with Sickle Cell Disease and other Hemoglobinopathies in the Brazilian national healthcare service [18].

The Brazilian Guidelines for Transcranial Doppler in children and adolescents with sickle cell disease, presented on **Table 1**, has established recommendations for the frequency of TCD according to the STOP study [18].

Table 1. Recommendations for the frequency of TCD according to the result of the examination.

Result of TCD	Cerebral Blood Flow Velocity (cm/s)	Frequency of exam
Absence of window	-	Use other imaging resource to analyze cerebrovascular events.
Technical difficulty due to lack of cooperation	-	Repeat every three months; evaluation by another examiner.
Low cerebral blood flow velocity	70	Repeat after 1 month.
Normal cerebral blood flow velocity	<170	Repeat annually.
Low conditional	Between 170 and 184	Repeat at three-month intervals. If the subsequent results are normal, adopt the normal conduct.
High conditional	Between 185 and 199	Repeat after 1 month. In case of unchanged examinations, it is recommended to repeat every three months. In case of two consecutive abnormal results, it is recommended to discuss the risk of strokes and consider a chronic transfusion regimen.
Abnormal	Between 200 and 219	Repeat after 1 month. If the velocity remains higher or equal to 200, it is recommended to discuss the risk of strokes and consider chronic transfusion regimen. If the result decreases to 170-199, it is recommended to repeat it after one month (if high conditional—between 185 and 199); or repeat it after 6 months (if conditional low—between 170 and 184). If the result is normalized (<170), it is recommended to repeat in 1 year.
	More than 220	Discuss imminent risk of strokes and consider chronic transfusion regimen.

TCD = transcranial Doppler, CBFV = cerebral blood flow velocity.

4. Conclusions

Hematopoietic stem cell transplantation is the only existing curative treatment for sickle cell disease, but the therapy depends on a compatible donor [13].

Several aspects have contributed significantly to the reduction in mortality in SCD patients. These include the control of infections through immunization and the prophylactic use of antibiotics during early life. Hydroxyurea therapy presents a risk of haematological toxicity, requiring strict monitoring of blood cell counts. In addition, the carcinogenic and teratogenic potential of the drug should be considered [21] [23] [27] [34] [45] [46].

It said that the clinical manifestations resulting from SCD are extremely variable among the patients, and the symptoms can range from asymptomatic to a very severe course, watchfulness and appropriate guidance for parents or caregivers is unquestionable. To recognize early signs of splenic sequestration, acute chest syndrome, and children at risk for developing stroke by using transcranial Doppler (TCD), and being able to provide packed red blood cell transfusions in the right time is the most common and feasible preventive measure for stroke in sickle cell disease.

Conflicts of Interest

The authors declare no conflicts of interest.

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