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THE EPIDEMIOLOGY, MANAGEMENT AND TREATMENT OF STROKE IN ADULTS WITH SICKLE CELL DISEASE.

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Abstract:

Stroke is a major contributing factor to the increase in morbidity and mortality rate in people with sickle cell disease (SCD). Stroke in more professional terms is known as a cerebrovascular accident. There are two main types of stroke, ischemic stroke and hemorrhagic stroke. Stroke can cause physical as well as cognitive deficits. Despite the high number of stroke cases in SCD patients, it still remains a poorly understood condition. Small or large vessel disease, chronic inflammation, altered cerebral autoregulation, hemolysis, and anemia (sickle cell disease) are risk factors for stroke. In this paper, we have reviewed the epidemiology of ischemic and hemorrhagic stroke in adults with sickle cell disease. We will also discuss the approach for its management (acute treatment and secondary prevention) and general risk factors.

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INTRODUCTION:

The presence of sickle cell disease (SCD) causes an increased risk of hemorrhagic and ischemic stroke. This association was first discovered and elaborated by Sdentricker in a young 3 year old boy with sickle cell disease and left hemiparesis.[1] Various analytical studies have shown that the prevalence of both types of stroke, hemorrhagic, and ischemic, is more common in adults with SCD than in the general population without SCD.

Sickle cell disease occurs due to a structural abnormality in the beta-globin chain of the hemoglobin molecule. SCD affects red blood cells (RBCs). In normal, healthy individual RBCs have a globular shape while in SCD the RBCs have a deformed sickle shape. This mutation is a single base change (GAT → GTT) on chromosome 11 in the sixth codon of exon-1 of the beta-globin gene. This change in base causes the synthesis of the beta-globin polypeptide of the hemoglobin molecule. Owing to this mutation valine acid replaces glutamic acid and results in the sickle cell hemoglobin (HbS) formation. This hydrophobic amino acid substitution forces the hemoglobin molecule to turn into a sickle shape when in the deoxygenated state, which in turns impair the transport of oxygen within the body.

These sickle-shaped cells cannot adapt to their environment, especially microvasculature. So these cells immaturely hemolyze and this leads to chronic anemia. Fever, dehydration, hypoxia, acidosis, stress, and a cold environment can exacerbate the condition of people with SCD. The anomalies of hemoglobin, endothelium, erythrocyte hydration, leukocytes, coagulation, vascular tone, and inflammatory responses can all lead to severe complications including stroke.

Epidemiology:

Sickle cell disease carries an increased risk of ischemic and hemorrhagic stroke. This predisposition has been confirmed in multiple case series.

Cooperative study of sickle cell disease (CSSCD) is the USA's largest multicenter observational study of complications of SCD. This study shows that the prevalence of stroke is 3.7% of all patients with SCD. The incidence of CVA (cerebrovascular accident) in patients with SCD varies with genotype. CVA is more common in the HbSS genotype as compared to other SCD genotype (HbSC, hemoglobin Sβ+ or Sβ0 thalassemia). CVA occurs in 11% of SCD patients under 20 years of age with genotype HbSS. In children, the highest incidence of stroke was found between the age of 2 to 5. [18]

According to CSSCD stroke is classified as hemorrhagic, ischemic, and transient ischemic attack (TIA). Ischemic stroke affects younger and older demographic while hemorrhagic strokes are more common in adults between the age of 20 to 29.

Different studies have looked at the mortality rate associated with stroke in SCD patients. Here we are going to have a look at the mortality rate of stroke in CSSCD and a study conducted in California. During the first 14 days, death due to ischemic stroke was uncommon in adults with SCD and ranged from 0% in the CSSCD to 8% in California. On the other hand, 24% of the children and adults with hemorrhagic stroke in the CSSCD died within the first 14 days, and 34% of adults died with hemorrhagic stroke in California. Intracerebral hemorrhage has a higher mortality rate (50–80%) as compared to subarachnoid hemorrhage (0–27%) in several case series. [19]

Studies have shown an estimated cumulative incidence of silent infarct as high as 37% in patients with SCD by 14 years of age. CSSCD has been classified into silent infarcts as an increase in T2 signal abnormality on multiple views on MRI without corresponding neurologic deficit. Criteria for silent infarct in pediatric patients requires an abnormality of at least 3 mm in greatest linear dimension visible on at least two planes of T2-weighted MRI sequences. 21.8% of children between the 6 to 19 years of age, having HbSS genotype were identified with silent infarcts.

The criteria for silent infarct in adults is a 5-mm signal hyperintensity in T2-weighted images with the corresponding hypointensity on the T1-weighted images due to the propensity for adults to naturally accumulate T2 hyperintensities as a function of the aging process. Different studies show varying a prevalence of silent infarct in adults. Some studies indicate almost 50% prevalence. More research is needed to comment on this issue. [20]

Risk Factors for Stroke

Occlusion of the microvasculature in organs can cause various morbidities in people suffering from SCD. While the vascular disease (stroke) of the brain is mainly caused by large vessel vasculopathy. MRI and CT scan evidence show that 80% of SCD related strokes occur in the major distal vessels of the brain.

Pediatric studies of SCD have generated a lot of data that has helped identify numerous genetic and clinical risk factors that can lead to stroke. [1] In children with SCD acute chest syndrome and aplastic crisis secondary to parvovirus infection

have a strong temporal association with ischemic stroke. On the other hand, it is still unclear if the previously mentioned factors increase the risk of stroke in adults. Ischemic stroke recurs in almost 67% of the untreated children with SCD. The majority of recurrent strokes happen within 24 months. A study has shown that children and young adults who were chronically transfused for childhood stroke had less incidence of recurrent stroke. Another studied compared the collateral effect of stroke and moyamoya (abnormal narrowing of the blood vessels in the brain) in children with SCD. The results showed that children with stroke and moyamoya are at increased risk of recurrent TIA and stroke (58%) compared to children with stroke and no moyamoya (28%). [2,4,5]

The following are the most commonly recognized major risk factor in adults for ischemic stroke, genotype (risk greatest for HbSS), hypertension, or high systolic blood pressure, acute chest syndrome (ACS). The risk factors for hemorrhagic stroke include older age, low steady state hemoglobin, and high steady state leukocyte count. Several other risk factors like diabetes mellitus, renal disease, hyperlipidemia and atrial fibrillation can also add to the risk of stroke in people suffering from SCD. [2, 4]

The clinical studies of the risk factors encompassing hemorrhagic stroke include high steady-state leukocyte count and low steady-state hemoglobin. Some risk factors leading to hemorrhagic stroke have been identified in adults, these include renal disease, hypertension and coagulation. [6] A controlled case study of 15 adults with hemorrhagic stroke and 30 with ischemic stroke was carried out. It was observed that the hemorrhagic stroke had a strong association with hypertension, acute chest syndrome, recent transfusion and treatment with corticosteroids. Multiple genes have also been found responsible for ischemic stroke in children and young adults. These genes (ANXA2, TGFBR3, TEK, ADCY9, HbA2 α-thalassemia 3.7 kb deletion) are characterized by the occlusion of the distal internal carotid or anterior cerebral and proximal middle arteries and a large vessel vasculopathy with stenosis. [7]

Evaluation of Suspected Stroke

The evaluation and management of stroke in SCD patients should be based on their medical history, traditional risk factors, current signs and symptoms. The chances of the occurrence of ischemic stroke in young patients with HbSS are more than in older adults with SC hemoglobin disease or sickle-β plus thalassemia. Almost 80% of ischemic stroke patients present with hemiparesis, 11% with seizure, and 58% with headache. Prominent impaired mental status, a headache and thinking issues are symptoms of stroke and more frequent 89% with hemorrhagic strokes. MRI of the brain, even though difficult to obtain on an urgent basis in most of the hospitals, provides the precise scans for both, ischemic and hemorrhagic strokes. CT scans of the brain, on the other hand, are highly sensitive for hemorrhagic stroke identification, but it may not be precise for acute ischemic stroke identification within the starting months of the onset of the symptoms. [8, 9]

Vascular imaging should be gathered in SCD patients with stroke. MRA (MR angiography) at the early hospitalization stage is most appropriate for the cerebral vasculature evaluation. In the general population of the adults, in addition to MRA of the brain and CT angiography of the neck and brain, it is reasonable to include duplex ultrasonography or MRA of the neck with gadolinium which aids in improving visualization of carotids. These techniques aids in the detection of obstructive vasculopathy and moyamoya that might will increase the risk of recurrent stroke. [10]

Digital subtraction arteriography is also recommended for adults with subarachnoid hemorrhage. Patients with SCD are at risk of stroke with the administration of hyperosmolar intravenous. However, this risk can be lower down with hydration, use of low osmolar contrast and transfusion to attain the Hb S level to <20–50% of total hemoglobin. A thorough investigation of other potential risk factors would be quite helpful in evaluating the cause of ischemic stroke in adults. Testing like TCD or echocardiology with saline agitation to screen for a patent foramen ovale, atrial fibrillation monitoring, cholesterol, LDL, HDL, triglycerides, screening for DM, usage of tobacco and drugs are all associated with stroke in SCD patients. [11]

Primary Stroke Prevention:

At this time there are no validated methods to screen for the increased risk of stroke in adults with SCD. On the other hand, Transcranial Doppler ultrasound (TCD) can help identify children with HbSS at an increased risk of stroke. The Stroke Prevention (STOP) trial demonstrated the efficacy of regular transfusion to maintain hemoglobin S (Hb S) <30%, to decrease the absolute risk of stroke by 30% over 30 months to 3%. More studies and research are needed to properly set up a protocol for the detection of an increase in the risk of stroke in people with SCD.

Treatment of Ischemic Stroke

The acute treatment for ischemic stroke is based upon the age and characteristics of the SCD patient.

Treatment with thrombolytic agents meet the accepted criteria in adults, but no reports are published yet stating that this treatment is fine for adults and children with SCD. Thus, an increased rate of intracranial hemorrhage can result in increased risk of complications. For this purpose, it is imperative to clearly discuss the issues and details with the family of the patients before the administration of any kind of drug or thrombolytic agents. [12]

The goals of ischemic stroke management are to minimize the injury from stroke, limit recurrence and attain secondary prevention. Limitation to injury includes the intervention of supportive measures for optimization oxygenation, ventilation, cerebral perfusion, normal normoglycemia and treatment of hyperthermia and cardiac monitoring.
The identified risks and approaches to secondary prevention guides in treatment of stroke, because every case varies. For instance, risk factor modification in patients with hypertension, DM, tobacco and hypercholesterolemia; anticoagulation in patients with strong indication, i.e. mechanical heart valve, concurrent pulmonary embolus; and carotid endarterectomy in symptomatic carotid stenosis, are a few scenarios. Antiplatelet therapy is promising for the treatment of acute ischemic stroke in adults, the 325 mg aspirin should be the first choice. Clopidogrel, aspirin, and ticlopidine and other antiplatelet agents have a role in secondary prevention. [13, 14]

These all agents; aspirin combined with ticlopidine and dipyridamole, are considered good for the small scale treatment of pain with SCD without increasing bleeding. However, these agents can increase the risk of hemorrhagic stroke in the general population. Stents can also be considered for use in the early days of hospitalization, as these may aid in reducing the recurrent ischemic stroke and TIA in SCD patients with ischemic stroke. Short term statins usage is safe in SCD patients, but its long term safety usage is unknown.

The alternative approach includes hematopoietic stem cell transplantation, hydroxyurea and revascularization. After alteast 6 months of transfusion, hydroxyurea can reduce the risk of recurrent stroke in young adults. Hematopoietic stem cell transplantation (HSCT) is considered a promising therapy in SCD patients for secondary stroke prevention.

Treatment of Hemorrhagic Stroke

The recognized treatment for acute hemorrhagic stroke in the general population: treatment in an intensive care unit, the reversal of anticoagulation or replacement of factor deficiencies, appropriate blood pressure management, and treatment of seizures with antiepileptic agents. Surgery is usually not mandatory for intracerebral hemorrhage patients. [15]

Patients with cerebellar hematomas with less than 3 cm in diameter have shown good outcomes with surgical evacuation. As there are no randomized studies found on a clinical basis, therefore it is widely accepted that the removal of hematoma and decompression in patients with cerebellar hemorrhage is beneficial and the patient should undergo surgery; The external ventricular drain is helpful in patients with acute hydrocephalus; the patients should have the surgery asap for the evacuation of hematoma if they have hydrocephalus owing to cerebellar hemorrhage. Delay may be harmful.

The identified cause of stroke like blood pressure in hypertensive patients or anticoagulation might be helpful in treating the stroke. No specific data on the utility of dedicated stroke units and rehabilitation of SCD adults is present. However, on the basis of given guidelines it is recommended that SCD stroke patients should be treated by both neurologists and hematologists. Evaluation for stroke rehabilitation and formal cognitive assessment should be included in the treatment plan, as this step is imperative. [16]

Limited data are present on clipping or coil embolization of aneurysm after subarachnoid hemorrhage, and on the basis of this limited data, it is recommended that standard management must be carried out. For acute intervention like a transfusion, aspirin or other platelet antagonists and secondary preventive techniques like hydroxyurea for stroke management in SCD patients should be carefully evaluated.

These studies depict that in every case, only careful evaluation and detection can define the right path for primary and secondary treatment for stroke in SCD patients. [17]

CONCLUSION:

The epidemiology of stroke with sickle cell disease is well defined in children, however, the data on adults is perplexing and frustrating, as complications increase with the increase in age. For ischemic stroke management and treatment, some data is present, but for hemorrhagic stroke very limited evidence has been found. Extrapolation from treatments is tempting for the general population. Research is imperative to provide evidence-based care for adults with sickle cell disease.

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