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ISCHEMIC STROKE AS AN OUTCOME OF SICKLE CELL ANEMIA IN CHILDHOOD: CASE REPORT

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Abstract: Sickle cell anemia results from a genetic alteration characterized by a mutant hemoglobin, hemoglobin S (HbS), which in its homozygous state causes distortion of erythrocytes. The decompensation of the disease occurs when this hemoglobin undergoes polymerization at the time it is deoxygenated, either due to a reduction in the oxygen concentration or due to factors that reduce the oxygen-hemoglobin bond, such as an increase in temperature or a drop in pH. Such an event can cause premature destruction of abnormal erythrocytes by the spleen and microvascular vasocclusion, causing tissue ischemia, acute pain and gradual damage to the affected organ. The ischemic cerebrovascular accident (CVA) is one of the most serious outcomes of this disease, which is 280 times more common in children with Sickle Cell Anemia. of an 8-month-old infant with Sickle Cell Anemia, who presented fever and prostration, requiring blood transfusion and evolving with 2 epileptic seizures, with an extensive CVA being evidenced in the cranial tomography. In order to elucidate the importance of the reported case, an active search of epidemiological data was carried out at a global and regional level, highlighting the prevalence of cases of sickle cell anemia at Hospital Alcides Carneiro in relation to age group, gender and reason for hospitalization. Finally, with the outcome of the case, the importance of screening and early diagnosis of this disease becomes evident, with a description of an initial approach protocol for children with sickle cell anemia who present with fever in the emergency room.
Keywords: Pediatrics; Brain stroke; Sickle cell anemia; Hematologic Diseases.

INTRODUCTION

Sickle cell anemia is a genetic alteration characterized by a type of mutant hemoglobin, hemoglobin S (HbS), which in its homozygous state causes distortion of erythrocytes, making them take the shape of a "sickle". The most common situation occurs when two people with sickle cell trait - with a genetic pattern represented by hemoglobin A (HbA) associated with hemoglobin S (HbS), and whose universal representation is HbAS - unite, constituting an offspring, the which has a 25% chance of having the HbSS genotype and manifesting the disease. This pathology is in the Neonatal Screening Program, and if it presents an altered result, it must be confirmed by carrying out hemoglobin electrophoresis in cellulose acetate or in agarose with alkaline pH. [1,5]

The decompensation of the disease occurs when the mutant hemoglobin (HbSS) undergoes polymerization at the time it is deoxygenated, either due to a reduction in the oxygen concentration or factors that decrease the oxygen-hemoglobin bond, such as an increase in temperature and a drop in pH. This way, a gelatinous network of fibrous polymers is formed, contributing to the stiffening of the erythrocyte membrane, increased viscosity and dehydration due to potassium leakage and calcium influx. These alterations are responsible for changing the conformation of red blood cells into a sickle shape and result in the loss of flexibility needed to cross the small capillaries. Such abnormalities can cause premature destruction of abnormal erythrocytes by the spleen (hemolytic anemia) and microvascular vasocclusion, causing tissue ischemia, acute pain and gradual damage to the affected organ.[5]

Among the complications related to vasocclusion, the following are mentioned in the literature: Acute Thoracic Syndrome, Painful Crisis, Stroke, Splenic Sequestration Crisis, Aplastic Crisis, Priapism, Extremity Ulcers, in addition to hepatic, renal, cardiac and ophthalmologic alterations. The outcome cited as one of the most serious is ischemic stroke (CVA), which is 280 times more common in children with Sickle Cell Anemia, in addition to 30% of cases presenting recurrence of the episode.[7]

IVA is a condition resulting from the interruption of blood flow in cerebral arteries, especially those of the anterior circulation, with repercussions in areas of ischemia and infarction. Neurological manifestations may vary according to the location of the ischemic event and the extent of the lesion involved, with the most reported being: hemiparesis or monoparesis, hemianesthesia, visual field defect, cranial nerve palsy, epileptic seizures, aphasia and coma. In the pediatric population, the clinical manifestations are diverse and generally nonspecific, which makes diagnosis difficult. Thus, children with at least one of the following criteria: (1) Acute onset of focal neurological deficit during any period; (2) Unexplained change in level of consciousness, especially when associated with headache; (3) Convulsions during the neonatal period and in the postoperative period in children undergoing cardiac surgery; must undergo an imaging method for diagnostic confirmation. Cranial computed tomography (CT) is considered by most authors as the best diagnostic study method due to its speed, practicality and availability, in addition to its ability to differentiate hemorrhagic events from ischemic events. [7]

The initial approach to stroke related to Sickle Cell Anemia includes: stabilization of vital signs, oxygenation, hydration and analgesia. In addition, immediate exchange blood transfusion must be performed with the aim of rapidly reducing circulating HbS levels in the blood to 30% and, if this is not possible, simple blood transfusion must be performed.

Secondly, promote the rehabilitation of the patient through physiotherapy and, in case of suspicion of an infectious focus, start antibiotic therapy according to the clinic.[4]

Long-term treatment aims at preventing new events of decompensation of Sickle Cell Anemia through: (1) Immunization and use of prophylactic Penicillin to avoid infections; (2) Folate supplementation to stimulate erythropoiesis; (3) Use of Hydroxyurea to increase circulating fetal Hb levels, decreasing the risk of vaso-occlusive events; and (4) allogeneic bone marrow transplantation.

In this context, the objective of this study is to report the case of an infant with sickle cell anemia who developed a large stroke, as well as the clinical manifestations presented and the therapeutic management offered. Documentation of this outcome is rare and of great importance, given the need for early recognition and rapid therapeutic institution, avoiding clinical worsening of the condition.

REPORT OF CASE

Infant, female, 8 months old, diagnosed with Sickle Cell Anemia without intercurrences since birth, started with unchecked fever, being attended at the Children's Emergency Unit where she was diagnosed with Acute Otitis Media and prescribed amoxicillin. After 2 days, the mother returned to the unit reporting persistence of the fever and was instructed to keep the previous prescription and return in 24 hours if the condition continued or worsened. The next day, the patient developed hypoactivity and intense prostration, and was taken to the Emergency Room again, where laboratory tests were requested that showed significant anemia: Hematocrit=12.2% (basal hematocrit= 26%), Hemoglobin= 4.4g/dL, Red blood cells= 1.46M/μL, CRP= 42.54mg/dL, white blood cells=27,190mm³ (0/0/0/0/8/79/10/3), platelets= 139,000/mm³ and reticulocytes=0.9% and chest X-ray without identified alterations. Immediate hospitalization, antibiotic therapy with amoxicillin + clavulanate 50mg/kg/day and blood transfusion 20ml/Kg were performed. Blood count after transfusion: Hematocrit=24.2%, Hemoglobin= 8.1g/dL, Red blood cells= 2.87M/μL and platelets = 131.000/mm³.

Ten minutes after the end of the blood transfusion, the patient developed a tonic-clonic epileptic seizure in the left side of the body, gaze deviation and alteration in perception, with diazepam 2mg in bolus. After the crisis improved, the patient evolved with deviation of the labial commissure, hemiparesis and anesthesia in the left side of the body. A maintenance dose of 5mg/kg/day of phenytoin was started and a transfer to Hemorio was requested. After 55 minutes, the infant had a new episode of epileptic seizures with tonic-clonic movements in the right side of the body, a phenobarbital attack was administered and a CT scan of the head was requested, which showed ischemic stroke (Figure 1).

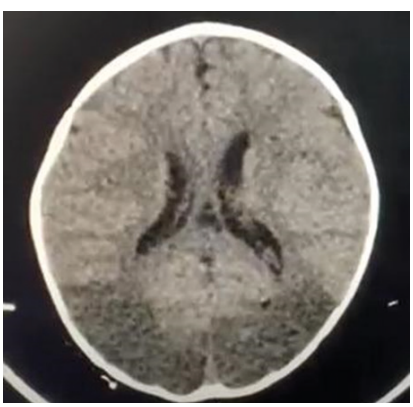

Figure 1 - Extensive area of bilateral parieto-occipital cortico-subcortical hypodensity, corresponding to ischemic insult/venous thrombosis. There are no signs of intraparenchymal bleeding, centralized midline and normal ventricles.

Source: Compiled by the authors, 2023

The following day, she was admitted to the neonatal ICU, with further laboratory

tests being carried out: Hematocrit=27%, Hemoglobin= 8.8g/dL, Red blood cells= 3.27M/μL, CRP= 85.03mg/dL, leukocytes=29,900mm³ (0/1/0/0/2/57/38/2), Platelets= 104,000, reticulocytes=1.2% and hemoglobin electrophoresis with 11.7% Fetal Hemoglobin and 36.2% Hemoglobin S. Abnormal elements of urine sediment, electrocardiogram and echocardiogram without significant alterations. In addition, a neurological evaluation was performed by a specialist with the following findings on physical examination: sleepy, but arousable to painful stimuli, with hypotonia and crural monoparesis on the left, grade 2 strength (does not overcome gravity), without further alterations. At the end of the day, transfer to Hemorio was performed and, for this reason, it was not possible to obtain more information about the case in question to describe the current status of the patient.

DISCUSSION

Sickle cell anemia originated predominantly in African populations and spread to different areas of the world.2 In 2010, it is estimated that around 300,000 children in the world were born with HbS homozygosity and 5 million with sickle cell trait.3 In Brazil, due to the strong influence of racial miscegenation, there was a significant increase in the frequency of this mutant allele, which contributed to sickle cell anemia becoming the most common monogenic hereditary disease in the country.[2]

In order to bring a regional epidemiological profile, the preparation of this case report covers data collected from the discharge book of the ward of Hospital Alcides Carneiro, Petrópolis-RJ in the last 5 years (04/23/2017 - 04/29/2022). During this period, a total of 5011 hospitalizations were registered, 29 of which were due to complications of sickle cell anemia and, of these 29 hospitalizations, only 10 patients were hospitalized more than once. When carrying out a more detailed analysis, it was observed: (1) the relation with the age group, being 48.3% of the hospitalizations of adolescents, 34.5% of schoolchildren, 13.8% of preschoolers and 3.4% of infants; (2) relationship with gender, with 80% of patients being male and 20% female; and (3) the reason for hospitalization, with 44.8% of hospitalizations due to painful crises, 27.5% due to infections, 6.8% due to hemolysis, 6.8% due to fever, 3.4% due to splenic sequestration and 10.3% not identified. With these data, it was possible to understand the profile of patients admitted to this institution due to complications of sickle cell anemia, with male adolescents being more common with decompensation of the disease due to pain crises or infections. Thus, it is clear that the patient in the reported case does not fit the most prevalent profile, as she is a female infant and had fever as the reason for hospitalization. Despite this, it is still necessary for health professionals to be able to identify and manage rare cases like this.

Regarding the outcome presented by the patient in question, studies were carried out that showed that stroke (ischemic or hemorrhagic) occurs in about 8% of children up to 14 years of age who have sickle cell anemia and do not follow a therapeutic plan and/or or prophylactic, confirming the importance of specialized monitoring.4

Management of acute stroke in Sickle Cell Anemia consists of ensuring hydration, supplemental oxygenation with the aim of achieving an O2 saturation greater than 95%, analgesia and, if the patient is febrile, starting antipyretics and prophylactic antibiotics. And the main measure to be taken is immediate exchange transfusion, with the purpose of reducing the HbS rate to less than 30%, in addition to increasing the supply of O2 through normal red blood cells. If it is not possible to perform an exchange transfusion,

a simple transfusion can be performed.6

It is noteworthy that interventions for the rehabilitation of patients who have had stroke episodes are carried out with the aim of minimizing sequelae and are based on three basic principles: adaptation, regeneration and neuroplasticity. Neuroplasticity is the alteration or reconnection of neural networks damaged by the ischemic or hemorrhagic insult and which, with favorable environmental stimuli and individual factors, can totally or partially replace the compromised functions. It can also be said that this brain plasticity is even more frequent in early childhood, with a peak up to 36 months of life, due to the greater capacity of the brain to model its structure and functioning. significant improvement in the neurological physical examination, since on the day of the occurrence of the epileptic seizures there was a change in motricity in both sides and, on the following day, only crural monoparesis on the left was evidenced, which indicates the expectation of a good evolutionary prognosis in terms of concerns the motor part.

The STOP experiment (Stroke Prevention Study in Sickle Cell Anemia) established Transcranial Doppler as a method for preventing strokes in children with Sickle Cell Anemia, in which the velocity of cerebral arterial blood flow is analyzed. Flow velocities greater than 200cm/s indicate a high risk for stroke and in these cases treatment with prophylactic transfusions is recommended, reducing HbS levels in the blood (goal <30%). This study proved that there was a 92% decrease in the risk of stroke with this screening.3

Another possibility of therapy is the use of Hydroxyurea, an antineoplastic drug that increases circulating levels of fetal hemoglobin (HbF) and also decreases the density of erythrocytes and their interaction with the endothelium, in a way that reduces the possibility of vaso-occlusive events. 3 Prophylactic immunization and penicillin can be used to avoid infections and consequent decompensation. As a last resort, bone marrow transplantation can be chosen, but there is not enough evidence to prove its effectiveness.

Furthermore, in this work a flowchart was built based on the fever protocol for children under 5 years old with Sickle Cell Anemia from the Ministry of Health. It aims to systematize the conduct in cases of children with Sickle Cell Anemia (Figure 2), so that to facilitate the identification of acute decompensation of the disease and allow early intervention, reducing the risk of more serious complications. Directing the investigation towards the request for complementary exams makes it possible to speed up the process and provide the most appropriate treatment.

Thus, based on the epidemiological data found and the importance of early diagnosis, Sickle Cell Anemia screening in the Neonatal Screening Program is notoriously of great relevance for public health in our country. Such action allows these children to be followed up by specialized centers for adequate treatment and management, thus avoiding possible complications of the disease.

CONCLUSION

This research leads us to conclude the importance of Sickle Cell Anemia screening by the Neonatal Screening Program and early diagnosis by pediatricians and general practitioners, culminating in a better prognosis for the child's recovery from the possible complications generated by the disease. Our project seeks to systematize the medical approach, in order to guarantee that the appropriate initial approach is taken, avoiding worse outcomes of the disease, and ensure that these children are followed up by specialized centers to carry out the correct treatment and management.

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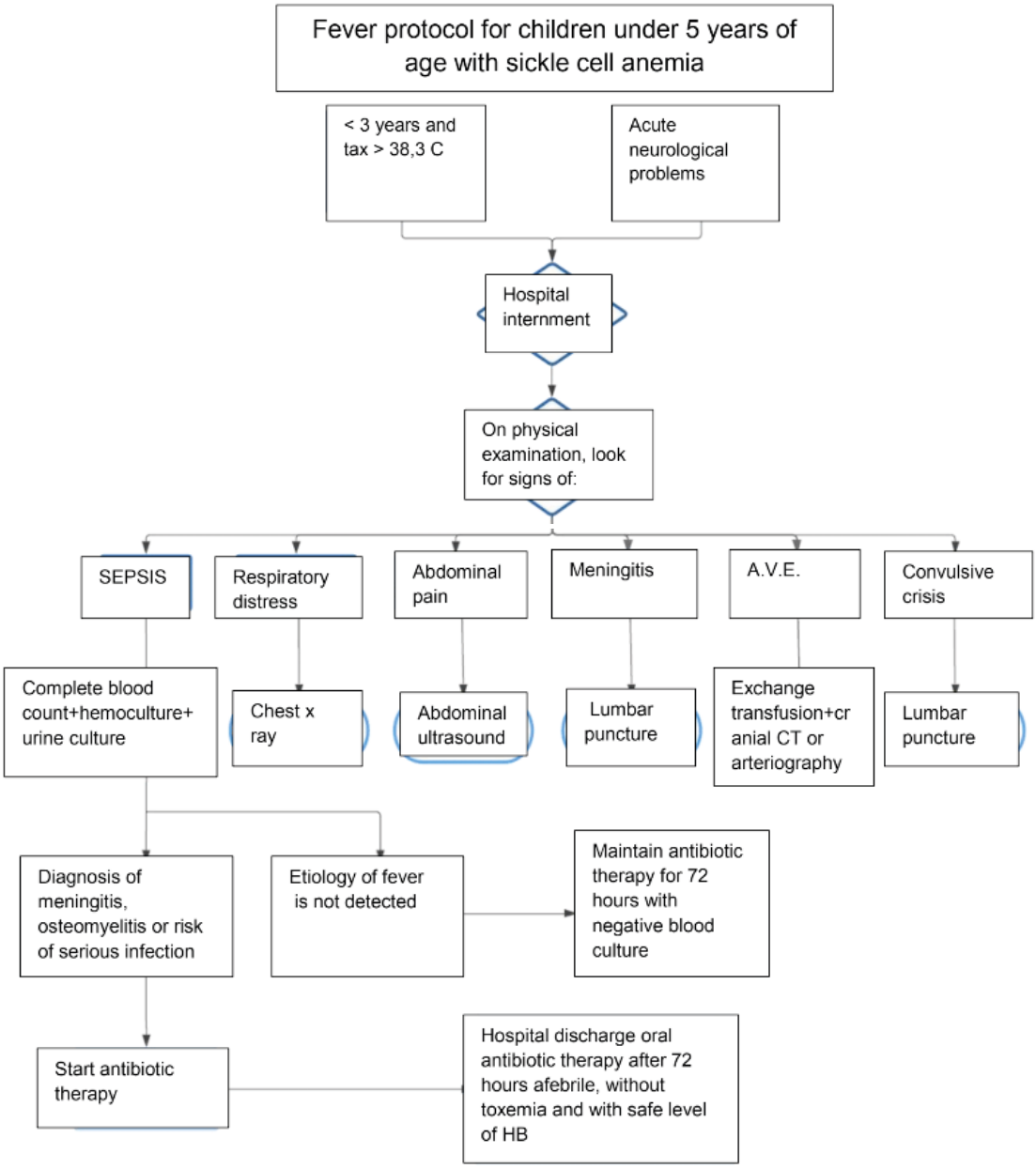

Figure 2 - This flowchart is based on the fever protocol for children under 5 years old with Sickle Cell Anemia in order to systematize the conduct in these cases. Thus, children under 3 years of age with an axillary temperature greater than 38.3ºC or children with acute neurological symptoms must be hospitalized. In the physical examination, attention must be paid to signs of Sepsis, Respiratory Discomfort, Abdominal Pain, Meningitis, Epileptic Crisis, CVA, among others, so that depending on the clinical condition presented by the patient, specific complementary exams must be requested, such as a complete blood count, chest X-ray, abdominal ultrasound, skull computed tomography (CT), lumbar puncture, blood transfusion, etc. If there is a diagnosis of Meningitis, Osteomyelitis or serious risk of infection, antibiotic therapy must be started. And if the etiology of the fever is not detected, the use of antibiotics is maintained for 72 hours with negative blood culture. Hospital discharge will only be allowed after 72 hours with oral antibiotics and only if the patient remains afebrile, without toxemia and with a safe hemoglobin level.[1]

Figure 2 - Fever protocol for children under 5 with Sickle Cell Anemia

Source: Elaborated by the author(2022)