0021-7557/09/85-02/163
Jornal de Pediatria

Acute splenic sequestration in a cohort of children with sickle cell anemia

Paulo V. Rezende,[1] Marcos B. Viana,[2] Mitiko Murao,[1] Ana Cristina Leite Chaves,[3] Ana Cristina F. Ribeiro[4]

Abstract

Objective: To analyze acute splenic sequestration (ASS) in children with sickle cell anemia diagnosed through a newborn screening program in the state of Minas Gerais, Brazil, and followed up at the hematology center in the city of Belo Horizonte, Minas Gerais, Brazil.

Methods: Retrospective cohort of 255 children with sickle cell anemia (Hb SS/Sβ^0) born between January 01, 2000, and December 31, 2004, and followed up until December 31, 2006. Data were abstracted from the patients' medical records.

Results: A total of 89 patients had 173 episodes of ASS (10.2 first episodes per 100 patient-years); 75% of the first episodes occurred before 2 years of age. The estimated probability of occurrence of the first episode of ASS during the study period was 40%. Recurrence rate reached 57.3%. After the first episode, splenectomy was indicated in only 12.4% of the cases; after the second, in 60.4% of the cases. After the third episode, 41.7% of the patients remained under clinical observation. The median time between indication for splenectomy and the actual surgical procedure was 2 months. During the intervening period, 37.2% of the children suffered a new episode of ASS and one child died. Case-fatality rate was 1.1% for the first episode and 7.8% for the subsequent episodes. Among a total of 255 children, 19 died: 36.8% due to infections and 26.3% after ASS.

Conclusions: ASS is relatively common in sickle cell anemia, mainly in the first 2 years of life; relapse occurs in more than half of the cases. Conservative management instead of immediate splenectomy was the method of choice. Although the case-fatality rate was low, ASS was the second most common cause of death. These results disclose some fragilities of the health system in the state of Minas Gerais and the need for better professional education to approach ASS crises.

J Pediatr (Rio J). 2009;85(2):163-169: Sickle cell anemia, acute splenic sequestration, children, splenectomy, newborn screening, mortality.

Introduction

Sickle cell disease is a global public health problem. In Brazil, the estimated number of individuals with sickle-cell trait is 7,200,000, with prevalence in the general population between 2 and 8%.[1] In the state of Minas Gerais, southeastern Brazil, the incidence of sickle-cell trait in the newborn statewide screening program (Programa Estadual de Triagem Neonatal, PETN-MG) is 3.3%.[2]

Acute splenic sequestration (ASS) refers to a common complication in children with sickle cell anemia. ASS is characterized by the pooling of red cells in the spleen, with a consequent increase in organ size and fall in hemoglobin levels.

1. Mestre. Serviço de Hematologia, Hospital das Clínicas, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil. Fundação Hemominas, Belo Horizonte, MG, Brazil.
2. Doutor. Professor titular, Departamento de Pediatria, Faculdade de Medicina, UFMG, Belo Horizonte, MG, Brazil.
3. Acadêmica de Medicina, Faculdade de Medicina, UFMG, Belo Horizonte, MG, Brazil.
4. Médica. Faculdade de Medicina, UFMG, Belo Horizonte, MG, Brazil.

Financial support: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq): Marcos B. Viana receives CNPq Research Grant 1D.

No conflicts of interest declared concerning the publication of this article.

Suggested citation: Rezende PV, Viana MB, Murao M, Chaves AC, Ribeiro AC. Acute splenic sequestration in a cohort of children with sickle cell anemia. J Pediatr (Rio J). 2009;85(2):163-169.

Manuscript received Dec 15 2008, accepted for publication Feb 04 2009.

doi:10.2223/JPED.1885

ASS is considered an important cause of death in the first decade of life, just second to infectious episodes.[3-7] The episodes show prevalence of 7.5 to 30%, occurring more frequently between 3 months and 5 years of age (76% before 2 years of age) and in patients with homozygous SS hemoglobinopathy.

The etiology of sequestration crises has yet to be defined. Blood flow is believed to divert through the intrasplenic shunts, causing growth of the organ, red blood cell retention and capillary engorgement.[4,8-11] There is no evidence of a seasonal pattern suggesting an infectious cause. Clinically, the episodes are considered a medical emergency: patients may show signs of hypovolemic shock, progressing to death within a few hours. Effective treatment consists of early diagnosis, clinical support and packed red blood cell transfusion. Some reports demonstrate high recurrence and mortality rates.[4,6-8,12-19]

There is still controversy concerning subsequent management. Options include: careful clinical observation, periodic packed red blood cell transfusion regimens and splenectomy. Clinical trials on ASS are retrospective, descriptive, noncontrolled and raise questions about the actual splenic function after the episodes, in addition to the pros and cons of splenectomy compared with chronic transfusions.[3,11,13,20,21]

National data on ASS crises are not available in papers published in indexed journals. In an attempt to fill this gap, the objective of this study was to analyze clinical, epidemiologic and treatment characteristics of ASS in children diagnosed through the PETN-MG and followed up in the outpatient clinic at the hematology center Fundação Centro de Hematologia e Hemoterapia de Belo Horizonte (Hemominas), in the state of Minas Gerais, southeastern Brazil.

Methods

A retrospective descriptive cohort study using data abstracted from the patients' medical records attended at Hemominas and from PETN-MG database. The initial population was composed of all 284 children with hemoglobin FS electrophoretic profile at birth (SS/Sβ^0), born between Jan 01, 2000 and Dec 31, 2004. The patients were followed up for clinical and laboratory progress up to Dec 31, 2006, so all children were followed for, at least, 2 years.

The study population included 89 case patients who had one or more episodes of ASS, defined as an episode entered on the medical record by the hematologist in charge of the child's follow-up. Record of each episode of ASS is performed based on the report cards of patients attending the emergency service, on which the physician reports episodes, management and progress of the child. The control group was composed of 166 children with no record of ASS, reaching a total of 255 patients analyzed.

Twenty-nine patients were excluded from the study, as follows: other electrophoretic profiles at 6 months of age (2 Sβ^+ thalassemia and 1 SD); 11 children who failed follow-up up to 2 years of age for any reason but death; and 15 patients referred to another state or another hematology center in the state of Minas Gerais up to 2 years of age.

Each child's medical record contained identification data, baseline hematologic data (hemoglobin, white blood cell count, platelet count, reticulocyte count and hemoglobin electrophoresis) and baseline spleen size on palpation at physical examination. All hematologic values were transferred from the medical records to the database, if the blood sample had been drawn in the absence of infectious process or pain crisis, and, at least, 3 months after the use of blood components. Arithmetic mean of each item was considered as the baseline value for each patient. Baseline fetal hemoglobin dosage was obtained from the hemoglobin electrophoreses recorded on the report card of each patient. We chose to consider the electrophoresis performed at a later age within the follow-up period, as long as it was performed after 12 months of age, when the physiological concentration of fetal hemoglobin was already relatively stable.

Regarding ASS, during a crisis, we assessed clinical (spleen size and associated symptoms) and the above-mentioned hematologic data, presence or not of medical care, crisis management, clinical progress and follow-up of these children. At occasional recurrences, the same data were collected.

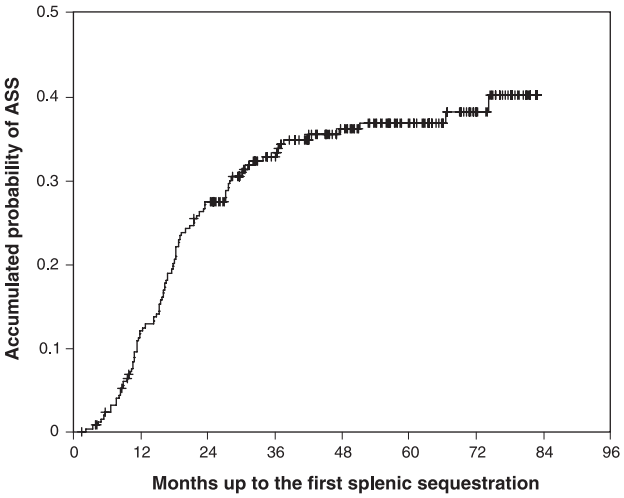
Information related to the patients who died were obtained from the medical records at Hemominas, from a copy of the death certificate provided by PETN-MG and from data of the interviews carried out by Fernandes,[22] described in her master thesis.

General mortality rate up to 2 years of age was obtained as a result of the number of deaths up to 2 years of age divided by the exposed population, since all patients had the opportunity to be followed up, at least, until this age.

The Kaplan-Meier method was used to determine the probability curve for occurrence of the first episode of ASS. The children who died were "censored", if death was not a result of the first episode of ASS, as well as the children who did not have an episode of ASS until the end of the study.

Associations of ASS occurrence (or not) with sex, town of residence (capital city or countryside), presence of baseline splenomegaly, hemoglobin level, percentage of fetal hemoglobin, and baseline leukocyte, platelet and reticulocyte counts were evaluated based on the chi-square and Fisher's tests for nominal variables and the Student *t* and Mann-Whitney tests for continuous variables, with normal or non-normal distribution, respectively. The tests were considered significant when an alpha error probability was ≤ 0.05.

The study was approved by the Research Ethics Committee of Hemominas, on Aug 07, 2006, protocol number 141.



ASS = acute splenic sequestration.

Figure 1 - Probability curve for occurrence of the first episode of acute splenic sequestration, according to the exposure time of each child (Kaplan-Meier method)

Results

A total of 255 children were analyzed, 123 (48.2%) were male and 132 (51.8%) were female. We identified 173 episodes of ASS, which occurred in 89 patients, with incidence of 10.2 first episodes per 100 patient-years. A single episode of ASS was identified in 38 patients; 51 patients had two or more episodes of ASS, with recurrence rate of 57.3%.

Age at first episode ranged from 2.3 months to 6 years and 3 months (median 16.6 months); 75% of these episodes occurred up to 23.5 months of age. The accumulated probability for occurrence of the first episode of ASS, over the entire study period, was 40% (Figure 1).

Only one child did not receive medical care during ASS. Patients were assisted mainly in tertiary hospitals in the city of Belo Horizonte or at Hemominas (57.8%); medical care in the countryside was recorded in 26.6%.

Baseline hematologic values as well as during the 173 episodes of ASS are summarized in Table 1.

Diagnoses associated with ASS were recorded for 91 episodes, infectious diseases being the most common association (89.6%). In 24 episodes, there was no association recorded and, in 58, the information was missing on the medical record.

The choice of management for acute episode was clinical follow-up or indication for splenectomy. None of the children were included in a chronic red blood cell transfusion program.

Fifty-one splenectomies were indicated for the 89 children who had ASS; 48 were actually performed. In two cases, the procedure was not authorized by the family. The patients remained under clinical observation and did not have new episodes of ASS. Another child, with indication for splenectomy after two episodes of ASS, had a new episode and died before the procedure was performed. Table 2 shows the indications for splenectomy, after each episode of ASS.

The median waiting time between indication for splenectomy and the actual procedure was approximately 2 months; 25% of the children waited longer than 5 months. In the intervening period between indication and actual surgery, 19 patients (37.2%) had a new episode of ASS and one of them died, as previously mentioned. Of these 19 children, two had 2 new episodes while waiting for the surgery.

In the study population (n = 255), 19 deaths occurred; seven of them associated with infections, five due to ASS, four of unknown cause, two of "respiratory failure", and one in a state of coma (possibly a cerebrovascular accident). Age at death ranged from 45 days to 5 years and 6 months (median 10 months). Mortality rate at 2 years of age was 5.1% [95% confidence interval (95%CI) 2.4-7.8]. Estimated probabilities of survival with 1, 2 and 5 years of age were 96.1 (95%CI 93.7-98.5), 94.9 (95%CI 92.2-97.6) and 92.4% (95%CI 88.8-96.0), respectively. Case-fatality rate by ASS for the first episode was 1/89 (1.1%, 95%CI 0-3.26) and for subsequent episodes 4/51 (7.8%, 95%CI 0.5-15.2).

Table 1 - Baseline blood tests of the patients included in the study, performed between 1 and 2 years of age, in the absence of infectious process or pain crisis, and at least 3 months after the use of blood components: laboratory assays during the 173 episodes of ASS

Blood test	Baseline	ASS
Hemoglobin (g/dL)	8.0 (7.4-9.1), n = 250	4.6 (3.8-7.5), n = 138
Leukometry (x 10^9/L)	14.4 (11.0-18.9), n = 250	17.5 (14.4-25.3), n = 71
Reticulocytes (%)	14.0 (8.5-16.8), n = 247	18.8 (17.0-21.3), n = 24
Platelet count (x 10^9/L)	357.7 (289.5-432.7), n = 250	110.5 (80.0-143.5), n = 82
Fetal hemoglobin (%)	21.0 (15.0-29.0), n = 230	-

ASS = acute splenic sequestration.

Table 2 - Indications for splenectomy in 89 children who had, at least, one episode of ASS

Indication for splenectomy	After 1st episode	After 2nd episode*	After 3rd episode	After 4th episode
Yes	11 (12.4%)	29 (60.4%)	7 (58.3%)	4 (100%)
No	78 (87.6%)	19 (39.6%)	5 (41.7%)	0 (0%)
Total	89	48	12	4

ASS = acute splenic sequestration.
* To calculate numbers after the second episode, children who suffered only one episode of ASS and those who were not submitted to splenectomy after the first episode of AAS, although recommended by the physician, were excluded. The same procedure was adopted to calculate numbers for the remaining episodes.

Table 3 shows associations between ASS and the variables analyzed.

Discussion

In the present study, the incidence of ASS was 10.2 first episodes per 100 patient-years, with recurrence rate of 57.3%. Similar incidence (8.2 and 9.2 first episodes per 100 patient-years) was found by other authors.[8,23] Regarding recurrence of episodes, the results from other authors are similar to those found in our study, with rates of 49, 50 and 71%.[8,13,14]

There was no statistically significant association between sex and development of ASS, similar to the findings by other authors.[4,6,8,12,14,24] Additionally, the higher frequency of ASS in infants was equally reported in other studies.[4,8-10,13-15,20,25]

The probability curve for occurrence of the first episode of ASS (Figure 1) indicates that 27.1, 33 and 37% of the children are likely to have suffered the first episode of ASS at the age of 2, 3 and 5 years, respectively. The Jamaican estimate,[8] using a similar methodology, was 22.5, 26.5 and

Table 3 - Factors associated with the development of ASS

Variable	Children with ASS	Children without ASS	p
Sex			0.78*
Male	44	79	
Female	45	87	
Town of residence			0.69*
Capital city	20	41	
Countryside	69	125	
Baseline splenomegaly			0.01*
Yes	51	67	
No	38	99	
Baseline hemoglobin (g/dL), median (25-75%)	7.9 (7.3-9.2)	8.1 (7.4-8.9)	0.58†
Baseline platelet count (x 10^9/L), median (25-75%)	359 (285.5-451.5)	360 (294-430)	0.96†
Reticulocyte count (%), median (25-75%)	14 (8.9-17)	14.2 (8.5-17.4)	0.92†
Baseline leukometry (x 10^9/L), median (25-75%)	12.9 (9.6-17.6)	15.4 (12.4-19.4)	0.001†
Fetal hemoglobin (%), median (25-75%)	19 (15-28)	23 (16-30)	0.03†

ASS = acute splenic sequestration.
* Chi-square test.
† Mann-Whitney test.

29.7% at 2, 3 and 5 years of age, respectively. In the American cohort,[12] estimates, at the same ages, were 8, 10 and 12%.

Regarding baseline hematologic values from laboratory examination and during the episodes of ASS (Table 1), other studies demonstrate results quite similar to those found in the present study.[4,6,25]

Regarding associated clinical factors, 52.6% of the episodes of ASS present some other associated clinical diagnosis, 89.6% being related to infectious diseases. A review of the literature shows that the etiology of ASS remains unknown. Some authors indicate a possible association with acute infectious processes, but could not establish a direct cause-effect relationship.[9,15,26]

The data presented in Table 2 demonstrate a clear convergence in the indication for splenectomy after two or more episodes of ASS. The majority of the authors, however, recommends splenectomy after the first[4,6,21] or, at most, after the second episode of ASS,[5,8,11,15] disclosing a trend toward a conservative management by the physicians in the present study, which may be influenced by the socioeconomic difficulties and lack of understanding of the families involved, as well as by the limited access to specialized care for such a surgical procedure. Data on the waiting time between indication for splenectomy and the actual procedure raise a worrying issue. The results reveal the sluggish performance of the Brazilian National Health System (Sistema Único de Saúde, SUS) and the existence of bureaucracy barriers that cause an unjustifiable delay in the process to actually carry out the surgical procedure.

Patients whose spleens were palpated below the left costal arch during some time of the follow-up presented approximately 2-fold increased risk of an episode of ASS in relation to those without splenomegaly. A similar result was found in Jordan.[14] No statistically significant association was observed between development of ASS and hemoglobin values, platelet count or reticulocyte count (Table 3), in accordance with data from the current literature.[8,14] However, children who did not have ASS showed fetal hemoglobin levels significantly higher than those with ASS. This association has already been described in several studies and is justified by the fact that red blood cells with a greater amount of fetal hemoglobin have lower levels of hemoglobin S, demonstrating less chance of sickling and, consequently, less probability of clinical manifestations.[8,10,11,27,28] Furthermore, a statistically significant association was observed between lower baseline leukometry and development of ASS. We could not find a similar result in the several articles searched in the current literature. The associations detected, although statistically significant, were weak and cannot accurately predict which child would more likely develop ASS, thus failing to have clinical relevance.

In the present study, general case-fatality of ASS was 5 deaths in 173 episodes of ASS (2.9%), much lower than that reported in the Jamaican cohort (9.8%).[8] However, the number of deaths of unknown cause (4/19 = 21.1%) was significantly high, which could mean underestimation of ASS case-fatality due to lack of recognition of this condition as a cause of death, as demonstrated in a study carried out with children at PETN-MG.[22]

The evaluation of the causes of the 19 deaths indicated the infectious processes as the main conditions leading to death (36.8%), followed by ASS (26.3%). Our findings are similar to the data published by some authors.[12,15,16,18,19,25] Among national data, the study by Fernandes[22] revealed that ASS was responsible, when the death certificate was used to determine death cause, for 13 (16.6%) of the 78 deaths, being the second most frequent known cause, following infectious complications. A study also carried out in the state of Minas Gerais, Brazil, demonstrated low adherence to prophylactic antibiotic therapy,[29] which partially explains these data.

Infant mortality for children with sickle anemia in the present study, regardless of having or not an episode of ASS, was 3.9%, i.e., 39/1,000 patients. According to the data from the Information System on Mortality of the Brazilian Ministry of Health (Sistema de Informações sobre Mortalidade do Ministério da Saúde), infant mortality rate in Minas Gerais in 2002 was 18/1,000. Deducting early neonatal mortality rates (deaths between 0 and 6 days of life, a period usually prior to newborn screening), mortality rate in Minas Gerais was 8/1,000, a value 4.8 times lower that that verified in the present study. This indicates that, even with an early diagnosis due to newborn screening, in Minas Gerais, the number of children with sickle cell anemia who die in the first year of life is higher than expected. A comparison between current and previous situation is not feasible because data are lacking.

The main limitation of this study refers to the accurate diagnosis of an episode of ASS, classically defined as a sudden increase in the splenic volume, associated with a drop of at least 2 g/dL in hemoglobin concentration and reticulocytosis. In a retrospective population-based study, it is impossible to reach such level of accuracy, since acute episodes, such as ASS, are diagnosed in several hospitals, polyclinics and primary health care units, making it impossible to recover all laboratory data. The protocol adopted was based, strictly, on the medical records of the hematology center, which could have either under or overestimated the incidence of ASS.

The present study brings into light some aspects on the situation of the children with sickle cell anemia in the setting of the Brazilian national health system. ASS is one of the most common clinical manifestations of children with sickle cell anemia, with marked features and a relatively simple diagnosis, which, in many situations, is not recognized because the medical team is not well-prepared, patient's family is not educated enough to deal with the problem, because of

socioeconomic difficulties, lack of safe and fast transportation of the affected children and lack of resources to immediately perform blood transfusion and basic hematologic tests. We cannot deny that some important steps to improve this situation have already been taken in several states and, in particular, in the state of Minas Gerais. Newborn screening for sickle cell disease, periodic training of the several health teams, introduction and publishing of specific protocols on the management of acute episodes of the disease, in addition to a multidisciplinary follow-up in specialized institutions and, especially, family education[8,25,30] are the hope to overcome difficulties in the short and the medium term.

It is evident that there is no simple solution for this problem, since it is not a simple problem. However, the present study alerts to the long way ahead. The program of total care to the individual with sickle cell anemia is a goal to be achieved by everyone involved in the problem, including managers, health professionals and family. Issues related to the disease should be recognized as a priority to the appropriate integral care, not of the sickle cell disease itself, but of children with sickle cell disease.

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Correspondence:
Marcos Borato Viana
Faculdade de Medicina - Departamento de Pediatria
Universidade Federal de Minas Gerais
Avenida Alfredo Balena, 190/267
CEP 30130-100 - Belo Horizonte, MG - Brazil
Tel.: +55 (31) 3409.9772
Fax: +55 (31) 3409.9770
E-mail: vianamb@gmail.com