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ORIGINAL ARTICLE

Clinical-epidemiological profile of pediatric patients with autoimmune hemolytic anemia in a center of reference

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Abstract

Objectives: The autoimmune hemolytic anemia (AIHA) is a group of diseases characterized by the presence of autoantibodies that bind to erythrocytes reducing the half-life of these cells. It is a rare condition that occurs in about 1-3 cases per 100,000 children per year, more common in males in ratio of 2:1 cases. This study aimed to obtain the clinical and epidemiological profile of pediatric patients diagnosed with autoimmune hemolytic anemia (AIHA), treated at the reference outpatient clinic. **Methods:** Participated in the study through analysis of medical records and completion of the research protocol 24 children with AIHA attended at the reference outpatient clinic between 2009 and 2019, age from 0 to 18 years. Clinical, laboratory and outcome data were obtained from patients records. **Results:** The results showed that most of the children are female (58%), receive early diagnosis until 2 years of age (58%). The direct antiglobulin test was positive in over 95% of cases. The patients presented cutaneous-mucous pallor (50%) as the initial symptom. However, the limitations inherent in the study, which had a small sample due to the rarity of the disease, should be evaluated. **Conclusion:** The diagnosis of AIHA must be made early, based on a detailed clinical history, suspected by the pediatrician through the characteristic signs of hemolysis and initiated treatment with corticotherapy, which shows high rates of remission and cure of the pathology.

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INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a group of diseases characterized by the presence of autoantibodies that bind to erythrocytes, reducing the half-life of these cells. It is a rare condition that occurs in about 1 – 3 cases per 100,000 children per year, being more common in males, at a ratio of 2:1 cases. However, in adolescents it is more common in females. There is no predisposition regarding race or relationship with consanguinity between parents[1-4]. Most diagnoses are made in the preschool phase, in the first 4 years of life[4,5].

AIHA can be divided into two types according to the type of autoantibodies involved. AIHA by warm antibodies is the most common type, occurring in about 70% of cases and manifests itself in body temperature (around 37ºC), usually by an immunoglobulin of the IgG type. The form caused by cold antibodies occurs in around 30% of cases, being activated by IgM immunoglobulin[3,4,6].

Another form of classification is as to primary and secondary. In primary AIHA, hemolytic anemia is the only laboratory finding and no systemic diseases are identified to explain the presence of autoantibodies. In secondary AIHA, autoimmune hemolytic anemia is just a manifestation of an underlying disease, such as systemic lupus erythematosus, lymphoproliferative diseases, drug exposure, after infections and in immunodeficiency states. It is worth mentioning that the main causes in childhood are viral and bacterial infections, while in adolescents it is more frequently associated with immunodeficiencies and autoimmune diseases[1,3-6].

The diagnosis is clinical and laboratory. The main complaints related to the disease are usually symptoms secondary to anemia in different degrees, such as asthenia, cutaneous-mucous pallor, jaundice and choluria. On physical examination, the most common symptoms are pallor and jaundice identified in the conjunctiva and palmar region, hepatomegaly and splenomegaly[7-9].

Laboratory tests may show hemoglobin often below 7 g/dL associated with hyperbilirubinemia at the expense of indirect bilirubin and elevation of lactate dehydrogenase (LDH). The absolute number of reticulocytes will be elevated, reflecting secondary medullary hyperplasia and peripheral erythrocyte destruction. Peripheral blood smears show the presence of spherocytes, schizocytes and polychromasia[1,6,10,11]. However, the most important test for the diagnosis of AIHA is the direct antiglobulin test (DAT), which will be positive in more than 95% of cases, also acting as a prognostic marker of the disease. It is noteworthy that in about 5% of cases the patient may have a diagnosis of autoimmune hemolytic anemia with a negative DAT, making the diagnosis a challenge for health professionals[4].

Treatment depends on the clinical severity and type of AIHA. The transfusion of packed red blood cells must be judicious due to the difficulty in finding a compatible type secondary to the concomitant hemolytic transfusion reaction[12].

The medication of choice for about 80% of patients according to the main guidelines will be corticosteroids, which will lead to a positive response to treatment in more than 80% of patients within three weeks of starting medication. Other treatment options used for patients who do not respond to corticosteroid therapy are intravenous immunoglobulin, splenectomy, cyclosporine, and rituximab with different responses to treatment, and plasma exchange in the case of AIHA by cold antibodies[7,8,12].

The present study will aim to obtain the clinical-epidemiological profile of patients diagnosed with Autoimmune Hemolytic Anemia between February 2009 and February 2019, treated at a referral outpatient clinic, aged between 0 and 18 years.

METHODS

Ethical aspects

The study was carried out according to the precepts of the Declaration of Helsinki and the Nuremberg Code, respecting the Norms for Research Involving Human Beings (CNS Resolution 466/2012) of the National Health Council and the research was only started after approval by the Ethics Committee with approval protocol 3,599,225.

Type of research

This is a descriptive, quantitative, retrospective cross-sectional study, applied to patients with a confirmed diagnosis of autoimmune hemolytic anemia, registered at the Fundação Centro de Hemoterapia e Hematologia do Pará (HEMOPA).

Study period

The study was carried out from March 2019 to December 2019.

Location and sample

The study was carried out at Fundação Centro de Hemoterapia e Hematologia do Pará, in the city of Belém, state of Pará, with patients diagnosed with autoimmune hemolytic anemia aged between 0 and 18 years.

Inclusion Criteria

Patients with a diagnosis of autoimmune hemolytic anemia aged between 0 and 18 years and diagnosed between February 2009 and February 2019, without distinction of color, social class and gender after signing the Term of Consent for the Use of Data (TCUD) were included in the research. by HEMOPA.

Exclusion criteria

Those who did not have a confirmed diagnosis of autoimmune hemolytic anemia, those over 18 years of age, those

who had another cytopenia or those who had their diagnosis before February 2009 and after February 2019 were excluded from the research.

Instruments and materials

The authors' own research protocol was applied to collect data from medical records.

Data collection

After the institution's acceptance, signature of the Term of Consent for the Use of Data and approval by the research ethics committee, data were collected by analyzing the medical records of patients diagnosed and treated in the period between February 2009 and February 2019 These data were transcribed into the research protocol performed by the researchers.

During the research, identification data such as sex, age and birthplace, as well as clinical data of each patient, were collected.

Data analysis

The data were initially tabulated and later statistically treated using the Bioestat 5.3 program.

RESULTS

The present study had 24 patients treated from 2009 to 2019 at the HEMOPA Foundation in the municipality of Belém in the State of Pará, of which most patients are female, 14 (58%), while males have 10 cases (42%).

Table 1 shows the percentage, by age group, of patients diagnosed with Autoimmune Hemolytic Anemia (AIHA) treated from 2009 to 2019 at Fundação HEMOPA. It is observed that 14 patients are in the range of up to 2 years of age (58%), however, the age groups with the lowest number of patients are those aged between 2 to 6 and 7 to 11 years with an equal distribution, 3 cases (13%).

Table 1. Number and percentage of patients, by age group, diagnosed with AIHA and who were treated from 2009 to 2019 at the HEMOPA Foundation.

Age Group	The amount	Percentage
up to 2 years	14	58%
2 to 6 years	3	13%
7 to 11 years	3	13%
12 to 18 years	4	16%
Total	24	100%

Source: Research Protocol.

Regarding the type of autoimmune hemolytic anemia, patients diagnosed with Autoimmune Hemolytic Anemia (AIHA) treated from 2009 to 2019 at the HEMOPA foundation. It is noteworthy that 12 (50%) patients had inconclusive tests, followed by patients with warm antibodies, which were 10 (42%) and mixed with 8% of cases.

As for the history of autoimmune disease, of the patients diagnosed with Autoimmune Hemolytic Anemia (AIHA) treated from 2009 to 2019. It is noted that 18 (75%) of the patients have no history of such diseases, while 6 (25%) have a history of systemic lupus erythematosus. The majority, 66% of patients, do not have other infectious-contagious comorbidities, followed by patients with Epstein-Barr virus (EBV) in 3 cases (13%) and HTLV with 2 patients (8%).

Table 2 shows the initial symptoms, in percentage and absolute numbers, of patients diagnosed with Autoimmune Hemolytic Anemia (AIHA) treated from 2009 to 2019. It is noted that 9 patients (38%) had mucosal pallor in isolation and 17 (70%) associated with another symptom at diagnosis, followed by jaundice (16%).

Table 2. Quantity and percentage of symptoms presented at diagnosis by patients diagnosed with AIHA and who were treated from 2009 to 2019 at Fundação HEMOPA.

Initial Symptoms	The amount	Percentage
Mucous skin pallor	9	38%
Jaundice	4	16%
Mucosal pallor/fever	4	16%
Fever	3	13%
Mucous skin pallor/Splenomegaly/Fever	1	4%
Mucous skin pallor/Splenomegaly	1	4%
Mucous skin pallor/Jaundice/Splenomegaly	1	4%
Mucous skin pallor/Jaundice/Fever	1	4%
Total	24	100%

Source: Research Protocol.

Table 3 shows the treatment performed, in percentage and absolute numbers, of patients diagnosed with Autoimmune Hemolytic Anemia (AIHA) treated from 2009 to 2019. It is noted that 12 (50%) of the patients were treated with prednisone alone (50 %) and that 22 (92%) of the patients responded to treatment and only 2 (8%) had no improvement.

DISCUSSION / CONCLUSION

Autoimmune hemolytic anemia (AIHA) is a disorder caused by the presence of autoantibodies that bind to red blood cells and reduce their half-life, being a rare condition in childhood. Between 2009 and 2019, 24 patients were followed up at the Fundação Centro de Hematologia e Hemoterapia do Pará (HEMOPA) with a confirmed diagnosis of this pathology.

Most patients are female (54%), disagreeing with the main studies that show a slightly higher prevalence for males,

Table 3. Quantity and percentage of treatments performed by patients diagnosed with AIHA and who were treated from 2009 to 2019 at Fundação HEMOPA.

Treatments performed	The amount	Percentage
Prednisone / Prednisolone	12	50.00%
Human Immunoglobin / Prednisone / Prednisolone / Pulse Therapy (Methylprednisolone)	7	29%
Human Immunoglobin / Prednisone / Prednisolone / Pulse Therapy (Dexamethasone)	2	8%
Human Immunoglobin / Pulse Therapy (Methylprednisolone)	1	4%
Prednisone / Prednisolone / Pulse Therapy (Methylprednisolone)	1	4%
Pulse Therapy (Dexamethasone)	1	4.17%
Total	24	100%

Source: Research Protocol.

but agreeing with others such as the one by Naithani in 2007. This difference can be explained by the higher prevalence in male patients. female in cases of secondary AIHA and in adolescents, being the second most prevalent group in our study, in addition to females having a higher prevalence of autoimmune diseases[7,8,4,14].

Most individuals were diagnosed with AIHA before the first six years of life, corresponding to 70% of cases. This result corroborates most of the studies on the subject, such as those by Wolowiec e Aladjidique (2015)[2], which showed an average age of diagnosis of less than six years, thus translating an early onset and diagnosis of the disease[4,5]. The present study was also similar to another Brazilian study on the subject, which presented a mean age of diagnosis at 10.5 months of life, leading to the belief that AIHA can manifest itself even earlier in the Brazilian population[1].

As for the direct antiglobulin test (DAT), it was present in more than 95% of the cases, in agreement with what has been reported by several other studies on the pathology, reinforcing this test as being of fundamental importance for the diagnosis of the pathology[2,4,7,9,10].

Regarding the type of AIHA found, in our study, half of the tests had an inconclusive result (50%). Such results can be interpreted by a limitation of the service in which the study was carried out, however, among the patients who tested positive, most correspond to warm antibodies, which is in agreement with the current literature that shows a higher prevalence of AIHA by warm antibodies[2,4,5,7,9,15].

In AIHA, the association with other diseases can occur. In the present study, 25% of the patients followed up had a diagnosis of Systemic Lupus Erythematosus (SLE) during the course of investigation and treatment, and about 12% had a family history of autoimmune disease (SLE), these numbers being higher than those found in all patients. other studies, however, reinforce the association of AIHA with autoimmune diseases, especially in adolescents[7-10,14].

AIHA can also be triggered by infectious diseases, with positive serology being found in 35% of the patients in our study, a result that is superior to the studies of the Mayo clinic in the United States and the French database on AIHA with 14% and 22% respectively, which can translate into a higher incidence of infectious diseases in our country, especially in the state where the research was carried out, where health care and socioeconomic conditions are still precarious[3,4]. The most prevalent infection is the Epstein-Barr virus, in agreement with other studies on the subject[3,4,16,17].

As for the symptoms found, the vast majority of patients had cutaneous-mucosal pallor as the main symptom at diagnosis, reported alone or in association with other symptoms in 70% of the patients followed up. Other symptoms such as fever and jaundice were also reported as initial complaints, which is in agreement with most studies carried out. This fact is due to the pathophysiology of the disease as a result of intense hemolysis[7-10,18].

The most used treatment was the use of prednisone/ prednisolone alone, which was performed in 50% of the patients studied, being in line with the literature as the first option for clinical treatment[8-10,13,19,20]. Other therapies used in our study for cases refractory to treatment with prednisone alone was the combined use of steroids with human immunoglobulin in 41% of patients. Such treatment is presented in the main *guidelines* as first-line therapy for refractory cases[1,3,13,20]. Other second-line treatments that were not used in any of the patients studied were rituximab , with efficacy rates of 84-100%, and splenectomy[20,21].

The mean treatment time was less than three months in 38% of the cases studied, showing the effectiveness of the use of corticosteroids as a first line, corroborating the literature that shows remission of symptoms in 80% of the cases within three weeks of treatment in several studies. treatment. It is possible that the longer time taken to control the disease was due to the difficulty in returning and patients' poor adherence to treatment after starting corticosteroids[3,10,12,20]. Among the 24 patients followed up, approximately 91% had a response to treatment with improvement in hemoglobin maintained after the end of corticosteroid therapy, and the two who did not have it because they were still in treatment during the research period or because of probable treatment abandonment.

However, the limitations inherent to the work, which presented a small sample due to the rarity of the disease, must be evaluated, which makes it difficult to find studies with high numbers of patients in a single research center. The fact that the study is retrospective also leads to certain limitations, as it depends on the correct completion of medical records and prevents the researchers from controlling the variables studied.

O The diagnosis of AIHA must be made early, based on a detailed clinical history, suspected by the pediatrician through the characteristic signs of hemolysis, and treatment with corticosteroids should be initiated, which has high rates of remission and cure of the pathology. Other pathologies

associated with the high prevalence of secondary AIHA should always be investigated.

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