Original Article

Emergency presentation and immediate outcome of children with autoimmune hemolytic anemia

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ABSTRACT

Aim: This study aims to analyze the clinical spectrum, severity of anemia, challenges in arranging cross matched blood in the emergency department (ED), and treatment outcomes of children with autoimmune hemolytic anemia (AIHA). **Methods:** Retrospective analysis was conducted in the tertiary care pediatric ED between October 2019 and September 2021. All direct antiglobulin test (DAT)-positive children were included in the study and those DAT negative were excluded from the study. The details regarding clinical condition, laboratory parameters, history of previous transfusion, difficulties related to cross-matching, requirement of steroid, and intensive care management were documented. **Results:** A total of 29 children were diagnosed to have AIHA. The most common clinical feature at diagnosis was fever (72.4%) followed by pallor (51.7%). Cross-matching was difficult for 9 children (31%) due various incompatibilities. Ten children required intensive care. Secondary causes were identified in 25 cases. Mortality was 10%. **Conclusion:** Identifying secondary causes of pediatric AIHA are essential and larger data from multiple centers will contribute toward creating the best clinical approach and emergency management of children with AIHA.

Key words: Anemia, Cross-matching, Hemolysis, Pediatric, Transfusion

Emergency presentation of autoimmune hemolytic anemia (AIHA) can be life-threatening as it rapidly worsens and needs to be identified early and treatment initiated immediately. AIHA is a rare and heterogeneous disease that affects 1–3/100,000 patients per year [1]. Autoimmune hemolytic anemia is the main cause of acquired extra corpuscular hemolysis in children. AIHA can be primary (or idiopathic) and secondary AIHA presenting with thrombocytopenia (Evans syndrome) which tends to have more chronic and relapsing clinical course. It is important that AIHA is considered in all children with acute onset of anemia ideally before transfusion of blood products. The diagnosis and management of children with AIHA presenting as an emergency involves many challenges related to laboratory methods, selection of blood products, and underlying primary disease [2]. This study presents data to highlight underlying issues in children with AIHA from a single-center pediatric emergency department (ED) in South India. We aim to analyze the clinical spectrum, the severity of anemia, challenges in arranging cross-matched blood in the ED, and treatment outcomes of children with AIHA.

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METHODS

This is a retrospective analysis of data from our digital medical records database. Children, less than 18 years of age diagnosed with AIHA, admitted to the tertiary care referral ED of Kanchi Kamakoti CHILDS Trust Hospital, Chennai, Tamil Nadu, between October 2019 and September 2021, were enrolled in the study. All direct antiglobulin test (DAT)-positive children were included in the study and those DAT negative were excluded from the study. The demographic details, presenting complaints, and laboratory parameters of all children were analyzed. Hemoglobin (Hb) level of <9 mg/dl was categorized as mild anemia, Hb between 3 and 6 g/dl was categorized as moderate anemia, and Hb <3 was categorized as very severe anemia [3]. AIHA was diagnosed based on the clinical presentation, a positive DAT. Polyspecific DAT test was performed routinely for all children with clinically suspected AIHA. The severity of AIHA based on DAT positivity was noted. Details of previous transfusion, difficulties related to cross-matching, the requirement of steroids, and intensive care management were documented. Details of treatment, duration of hospital stay, final diagnosis, and mortality were captured. The outcome was categorized as survivors or non-survivors. Simple descriptive statistics were used in this observational study.

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RESULTS

Our study cohort consisted of 29 children aged 1 month–18 years and three among the group were non-survivors. The median age of the survivors' group was 4.5 years and the non-survivors group was 12 years. Females constituted 65.5% of the study population. The most common clinical feature at diagnosis was fever (72.4%) followed by pallor (51.7%), fatigue (24.1%), jaundice and skin rash (20.7% each), bleeding manifestations in 17.2%, and joint pain in 6.9% of children.

Positive DAT was 4+ in two children, 3+ in nine children, 2+ positive in six children, and 1+ positive in 12 children. The median Hb values were 6.4 and 6.5 g/dl among survivors and non-survivors groups, respectively. Mild, severe, and very severe anemia were observed in 20.7%, 65.5%, and 13.8%, respectively. Median lactate dehydrogenase among the survivors' group was 950 U/L and the non-survivors group was 2501 U/L.

Thrombocytopenia was present in 44.8% of patients. Reticulocyte count was available for 44.8% of cases of which 3.4% of them had reticulocytopenia. Immunoglobulin and complement levels were available for 16 children. Immunoglobulin M mediated (IgM) in one case and solely immunoglobulin G mediated (IgG) in one case. We found mixed types in 14 with high IgG values and comparatively low IgM, IgA, C3, and C4 levels. The median IgG value was 2167 mg/dl. There were no significant clinical features relating to the type of immunoglobulins or complement levels.

Nearly two-thirds of children (17.2%) had received a previous packed red blood cell (PRBC) transfusion. Cross-matching was difficult for 9 children (31%) due to various incompatibilities. Intravenous steroid was initiated in the ED for 20.7% of cases. About 34.5% (n=10) of cases required intensive care treatment.

The reasons for transfer to the intensive care unit (Table 1) were cardiorespiratory failure (6.9%), severe anemia with congestive cardiac failure (6.9%), diphtheritic myocarditis with acute kidney injury (3.4%), fulminant hepatic failure (3.4%), severe thrombocytopenia with intracranial hemorrhage (3.4%), respiratory distress (3.4%), and very severe pneumonia (6.9%).

AIHA was classified as primary (idiopathic) in 4 cases (13.7%). AIHA was secondary (Table 2) in 25 cases (86%) such as infection triggered (n=9), systemic lupus erythematosis (n=7), connective tissue disorder (n=3), Evans syndrome (n=2), Wilson disease (n=1), acute leukemia (n=1), neonatal diabetes (n=1), and pure red cell aplasia (n=1).

Table 1: Reasons for transferring cases to PICU

Reasons for transferring cases to PICU	Numbers
Cardiorespiratory failure (6.9%)	2
Severe anemia with congestive cardiac failure (6.9%)	2
Diphtheritic myocarditis with acute kidney injury (3.4%)	1
Fulminant hepatic failure (3.4%),	1
Severe thrombocytopenia with intracranial hemorrhage (3.4%)	1
Respiratory distress (3.4%)	1
Very severe pneumonia (6.9%)	2

PICU: Pediatric intensive care unit

All three non-survivors had secondary AIHA. Treatment modalities included blood transfusion (n=23), intravenous immunoglobulins (IVIG, n=1), steroids (n=12), combination of IVIG and steroids (n=4), and supportive management (n=6).

The choice of treatment was based on etiology, the severity of the disease, and the child's response to therapy. None of them required plasmapheresis or splenectomy.

DISCUSSION

Children with AIHA usually present as an emergency. It is important to understand the clinical presentation, severity, and etiology of AIHA for optimal management. The age distribution of children with AIHA varies significantly in various studies and can be attributed to variation in demographic characteristics [3,4]. We observed that the median age of survivors was 4.5 years and 12 years in non-survivors. Fever as a presenting symptom, associated with pallor and jaundice, a common finding in our study, has been described in primary AIHA in children [5].

Data by Fan *et al*. showed that primary AIHA accounted for 39.7% and secondary AIHA accounted for 60.3% [3]. The availability of newer diagnostic tests could be a reason for secondary AIHA being more common (86%) in our cohort and the majority were infection associated. French National observational study has identified secondary AIHA in 63% of cases [6].

AIHA caused by warm autoantibodies (w-AIHA) antibodies that react with their antigens on the red blood cell optimally at 37°C, is the most common type, comprising 50% of pediatric cases [1]. About half of the w-AIHA cases are primary without specific etiology, the rest are secondary to other recognizable underlying disorders. IgG antibodies were predominant in our cohort indicating secondary causes.

A mean Hb of 6.1 g in our cohort is concurrent with other observations. Hb of <6 g/dl has been one of the predictors of outcome, especially in those who relapse or are refractory to the treatment of AIHA [7,8]. Thrombocytopenia observed in about 45% of our cohort is associated with immune deficiency, especially as a part of Evans syndrome [9]. Reticulocytopenia in AIHA can occur due to increased surface autoantibodies and reactive oxygen species on their surface, causing preferential clearance from the circulation [10]. DAT can be influenced by recent blood transfusions and needs to be considered in the interpretation of the test. Immunoglobulins, complements, and

Table 2: Secondary causes of AIHA and the number of cases

Secondary causes of AIHA	Numbers
Infection triggered	9
Systemic lupus erythematosis	7
Connective tissue disorder	3
Evans syndrome	2
Wilson disease	1
Acute leukemia	1
Neonatal diabetes	1
Pure red cell aplasia	1

AIHA: Autoimmune hemolytic anemia

thermal characteristics also influence the course of disease and treatment [7]. No correlation was found between response to treatment and parameters such as age, gender, jaundice, low pre-treatment Hb, reticulocyte count, platelet count, and subtype of AIHA [8]. Incompatibility of blood is reportedly common in warm antibody AIHA, hence, extended red cell genotyping and studies of antibody specificity should be undertaken before the first transfusion. In cold antibody cases, the use of a bedside blood warmer is helpful. We experienced difficulties in arranging a cross-matched sample for nine children. A literature review reveals that the "best match" or "least incompatible units" can be transfused to such patients under close supervision without any serious side effects [8]. In an emergency, transfusions should not, however, be deferred due to the non-availability of the "least incompatible unit" as the risk of allergic transfusion reactions is low [9]. Special techniques such as elution, which is the removal of antibodies from cells, and absorption, which is the removal of antibodies from serum, may be used to separate the mixture of antibodies [11]. Glucocorticoid is the initial emergency treatment with or without blood transfusion, to reduce hemolysis and stabilize Hb, and IVIG is often required if the response to steroids is poor. Rapid response and a greater experience in using and managing side effects favor glucocorticoids as first-line therapy. The dose and route of administration of glucocorticoids depend on the severity of anemia and clinical condition. Not much data are available regarding the role of IVIG in AIHA and Evans syndrome and can be added to treat children with severe illnesses with thrombocytopenia [10,12]. Cardiovascular complications of severe anemia and secondary causes contribute to the need for intensive care in children with AIHA. Early identification and emergency management with support from a well-equipped transfusion facility probably contributed to a good outcome in terms of mortality.

Follow-up of patients and details of antecedent hemolytic events were not included and are a limitation in our study.

CONCLUSION

AIHA is a life-threatening disease condition and necessitates emergency treatment. Identifying the secondary causes etiology and its level of severity will mitigate its occurrence, thus help tailor a treatment. Further studies are recommended in this direction for better understanding and implementation.

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