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Autoimmune Hemolytic Anemia in Children: Clinical Profile and Outcome

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ABSTRACT

Autoimmune Hemolytic Anemia (AIHA) is an idiopathic condition marked by red blood cell destruction. **Objective:** To compare the clinical features, laboratory parameters, treatment approaches, and responses between idiopathic and secondary AIHA in pediatric patients, with the aim of identifying key distinctions that can inform the development of tailored diagnostic and therapeutic strategies. **Methods:** This was cross sectional study and conducted for six months from April 2024 to September 2024 at Department of pediatrics at Khairpur medical college khairpur mirs. Data were collected on demographics, presenting symptoms, laboratory findings (hemoglobin, bilirubin, LDH levels), antibody profiles, and treatment outcomes. SPSS 23 was used for statistical analysis to compare treatment responses and clinical characteristics between idiopathic and secondary AIHA patients. Chi-square tests were used for categorical variables and t-tests for continuous variables. **Results:** The mean age of participants was 6.8 years, with 58% male. Patients with idiopathic AIHA had higher hemoglobin levels (7.5 g/dL versus 6.9 g/dL for secondary, p=0.03) and lower bilirubin (3.6 mg/dL versus 4.1 mg/dL, p=0.02). Treatment varied significantly: 89% of idiopathic patients received steroids compared to 86% of secondary patients. Secondary patients were more likely to receive IVIG (51% versus 34%, p=0.04) and rituximab (37% versus 11%, p<0.01). Complete response rates were higher in idiopathic AIHA (83% versus 63%, p=0.01). **Conclusions:** Significant differences exist in the clinical presentation and treatment responses of idiopathic versus secondary AIHA. Tailored treatment strategies on AIHA type are essential for improving patient outcomes, warranting further research into these distinctions and new therapies.

INTRODUCTION

Autoimmune Hemolytic Anemia (AIHA) is a hematological condition defined by the premature death of red blood cells caused by the immune system's erroneous attack on them. This illness can cause major morbidity and, in severe situations, fatality, particularly in pediatric populations. AIHA in children can be divided into two categories: idiopathic and secondary. Idiopathic AIHA has no obvious cause, whereas secondary AIHA is caused by underlying illnesses such as infections, cancer, or autoimmune diseases[1]. The clinical manifestations of AIHA in children are pallor, jaundice, fatigue and splenomegaly; based on the degree of hemolysis and general condition of a child these can be mild or severe. It is important to diagnose AIHA as soon as possible; untreated, the disorder may cause life-threatening complications, including organ failure and impaired immunity [2]. Corticosteroids, including prednisone, are often the initial treatment choice for autoimmune hemolytic anemia. These medications work by suppressing the immune system and reducing inflammation. The initial approach to rapidly treat the symptoms of anemia is to start at a high dose of corticosteroids. Often within days or weeks, patients will see a response characterized by an increase in hemoglobin levels and reduction of hemolysis. The dose of corticosteroids can be tapered gradually as symptoms improve to minimize unwanted side effects. However

chronic administration of corticosteroid can lead to life threatening side effects like weight gain, increased risk for infection, osteoporosis and metabolic derangement (like diabetes) [3]. When corticosteroids alone have not produced the desired effect in patients with AIHA who are steroid-dependent, an immunosuppressive medication called azathioprine may be given. By preventing DNA synthesis, azathioprine inhibits the growth of immune cells that create autoantibodies against red blood cells [4]. Usually, it is applied as a second-line therapy, especially for persistent AIHA. Azathioprine can cause side effects such as liver toxicity, bone marrow suppression, and an increased risk of infections, even though it is beneficial for certain people. Throughout treatment, routine blood count and liver function testing is crucial [5, 6]. Splenectomy, or the surgical removal of the spleen, may be considered in cases of AIHA that do not respond well to medication therapy. Red blood cell survival and hemoglobin levels can be increased by eliminating the spleen, which is involved in a major portion of the breakdown of red blood cells. For patients with warm AIHA, this method is quite helpful. Splenectomy is not appropriate for every patient, and before undergoing this surgical procedure, one must carefully weigh the advantages and disadvantages [7]. In children, type secondary is frequently associated with lymphoreticular malignancy, autoimmune disease, primary immunodeficiency and rare drugs. Around 80% of kids have an intense and also self-limiting illness, that often improves with treatment for only a few days with steroids. In the presence of systemic disease, it takes a chronic relapsing course requiring prolonged immunosuppression. Secondary Autoimmune Hemolytic Anemia (AIHA) is not a disease in itself but a manifestation of other underlying disorders. Often associated with lymphmotoreticular malignancies; these neoplasms may', however, impair immune system function and create autoantibodies against red blood cells Lymphomas and leukemias [8]. This means that some cases of AIHA can occur due to immune systems gone haywire, which attack their own tissues including red blood cells (as is the case with autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus [SLE]). Furthermore, in individuals with primary immunodeficiency disorders, impaired immunity may lead to production of autoantibodies and subsequent development of secondary AIHA [9]. Some less common medicines that can cause AIHA include nonsteroidal anti-inflammatory drugs (NSAIDs), some anti-seizure drugs and antibiotics. These therapies stimulate an immune response that misidentifies red blood cells as targets. Because hemolytic anemia can improve with treatment of the underlying disease, knowledge of secondary AIHA triggers, and specific therapy for the respective trigger is important in optimizing therapy and management [10].

While previous studies have focused on either idiopathic or secondary AIHA individually, there is a lack of direct comparisons between these two forms, particularly in the pediatric population. This study aims to fill this gap by providing a comprehensive analysis of both forms of AIHA, thereby aiding clinicians in better understanding the distinct clinical and laboratory profiles, treatment responses, and management strategies for each type. These findings may help guide more personalized and effective therapeutic interventions for children with AIHA. The aim of this study was to shed some light on the demographic, clinical, laboratory data and management and outcome in children with AIHA. With this information, we hope to achieve an awareness and a better understanding of the incidence among children affected.

METHODS

This was cross sectional study and conducted for six months from April 2024 to September 2024 at Department of pediatrics at Khairpur Medical College, Khairpur Mirs. A consecutive sampling method was used to select pediatric patients diagnosed with autoimmune hemolytic anemia. Inclusion criteria were: age between 1 and 18 years, direct Coombs test positive, hemolysis raised bilirubin level, decreased haemoglobin levels and increased reticulocyte count. Exclusion criteria: Patients with hemolytic anemia due to other known reasons (for example, hereditary spherocytosis, glucose6-phosphate dehydrogenase lack of ability and/or medicine created hemolysis). The sample size calculation on prevalence: $n = Z2 \times p \times (1-p) / d21$, $Z = 95\%$ (1.96), p = Prevalence assumed (10%) for AIHA in pediatric hospitalized patients) and d = margin of error (5% or 0.05). Consequently, a sample size of at least 138 cases was needed. Demographics, presenting symptoms (such as pallor, jaundice, and hepatosplenomegaly), and laboratory parameters (such as hemoglobin levels <11 g%, total bilirubin >1.2 mg/dL, LDH >280 U/L, Reticulocyte count >2.5%, Coombs test results, and antibody profiles) were recorded during the review of medical records and direct patient assessments. The methods of treatment were also recorded, including the kinds of medication administered (rituximab, plasmapheresis, intravenous immunoglobulin (IVIG), steroids), the length of the steroid therapy course, the need for transfusions, and the length of hospital stay. Treatment responses were classified as total or partial, and any relapses were noted during the follow-up. Data were analyzed using SPSS. 23. Descriptive statistics (mean, standard deviation, frequency, percentage) summarized demographic and clinical characteristics. Independent t-test for comparing continuous variables (e.g., age, hemoglobin levels) between the two groups, assuming normal distribution of data. Chi-square test for categorical variables (e.g., gender, response to treatment) to

determine the association between group status and clinical outcomes. A p-value of <0.05 was considered statistically significant. The ethical approval for this study was obtained from the Ethical Review Board and the approval letter was issued under reference number [KMC/RERC/104].

RESULTS

The data highlighted the differences between idiopathic and secondary AIHA in terms of demographic features, clinical presentation, and laboratory findings. Table 1 reveals the descriptive statistics of study variables for n=138 patients. The average age of participants was 6.8 ± 2.4 years, suggesting that children in this sample were mainly in lower primary grades. The patients had a mean hemoglobin level of 7.1 ± 1.5 g/dL, indicating a notable degree of anemia in this population. The mean total bilirubin was 3.8 ± 1.2 mg/dL, which by definition constituted mild hyperbilirubinemia. While the mean hospital stay was 8.2 ± 3.5 days, indicating the clinical severity and complexity of patient management they reflected. Demographic characteristics showed a preponderance of male patients 80 (58%) versus female patients 58 (42%) for the cohort. The most common presenting symptom was pallor 127 (92%) patients and other frequent findings included jaundice 108 (78%) patients and hepatosplenomegaly 48 (35%). The types of Autoimmune Hemolytic Anemia (AIHA) were analyzed and 89 (64%) of the patients had idiopathic AIHA, while secondary AIHA was found in 49 (36%). These results described the clinical and demographic characteristics of the patient population within this study, noting also a significant presence of anemia and related symptoms.

Table 1: Descriptive Statistics of Study Variables (n = 138)

Variable	Mean ± SD / Frequency (%)
Age (Years)	6.8 ± 2.4
Hemoglobin (Hb) (g/dL)	7.1 ± 1.5
Total Bilirubin (mg/dL)	3.8 ± 1.2
Hospital Stay (Days)	8.2 ± 3.5
Gender	
Male	80 (58%)
Female	58 (42%)
Presenting Symptoms	
Pallor	127 (92%)
Jaundice	108 (78%)
Hepatosplenomegaly	48 (35%)
AIHA Type	
Idiopathic AIHA	89 (64%)
Secondary AIHA	49 (36%)

Descriptive analysis, frequency and percentage;

P<0.005 indicate significant values;

Bar graph represented the Etiological Spectrum of Secondary Autoimmune Hemolytic Anemia (AIHA). Infections would have the tallest bar, followed by Autoimmune Disorders and Malignancies, illustrating their significance as leading causes (Figure 1).
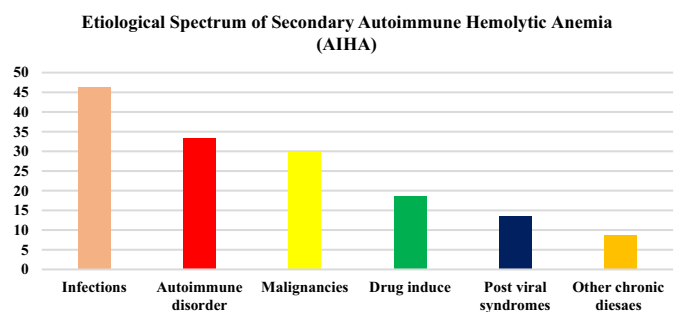

Figure 1: Etiological Spectrum of Secondary Autoimmune Hemolytic Anemia (AIHA)

Table 2, revealed that the examining laboratory parameters and antibody profiles between patients with idiopathic versus secondary AIHA is shown in Table 2. In total, 138 patients were recruited, with 64 having idiopathic AIHA and 41 (39%) secondary AIHA; the mean hemoglobin level was significantly higher in the former (hemoglobin A1c g/dL [0.13 mmol/L]): idiopathic: 7.5 versus secondary: 6.9 (P =.03). Furthermore, total bilirubin level (3.6 mg/dL versus 4.1 mg/dL) was lower in idiopathic AIHA than secondarily-related AIHA (p=0.02). Reticulocyte count was 4.5% on average (range, 2-25%) in idiopathic cases and 5.0% (2-20%) in secondary cases but this difference did not reach significance level (p = 0.09). Lactate dehydrogenase (LDH) levels were notably lower in the idiopathic group (620 U/L) than in the secondary group (780 U/L), with a p-value of 0.01, indicating a significant difference. When assessing the antibody profiles, the direct Coombs test positivity was similar in both groups, with 81% of idiopathic cases and 82% of secondary cases testing positive (p = 0.87). However, a higher percentage of patients with secondary AIHA tested positive on the indirect Coombs test (57%) compared to those with idiopathic AIHA (40%), approaching statistical significance (p = 0.05). The presence of warm antibodies (IgG) was slightly higher in idiopathic AIHA (79%) than in secondary AIHA (69%), but this difference was not statistically significant (p = 0.18). Cold antibodies (IgM) were found in 21% of the idiopathic group and 31% of the secondary group (p = 0.23). Notably, a mixed antibody profile was more prevalent in secondary AIHA, with 16% of patients exhibiting this profile compared to 6% in idiopathic cases, achieving statistical significance with a p-value of 0.04. Overall, these findings suggest that there are significant differences in certain laboratory parameters between idiopathic and secondary AIHA, particularly in hemoglobin, bilirubin, and LDH levels, as well as in the prevalence of mixed antibody profiles.

Table 2: Comparison of Laboratory Parameters and Antibody Profile in Idiopathic versus Secondary AIHA (n=138)

Variables	Idiopathic AIHA Mean ± SD/N (%)	Secondary AIHA Mean ± SD/N (%)	p-value
Hemoglobin (g/dL)	7.5 ± 1.3	6.9 ± 1.7	0.03
Total Bilirubin (mg/dL)	3.6 ± 1.1	4.1 ± 1.3	0.02
Reticulocyte Count (%)	4.5 ± 1.2	5.0 ± 1.4	0.09
LDH (U/L)	620 ± 220	780 ± 250	0.01
Direct Coombs Test Positive	72 (81%)	40 (82%)	0.87
Indirect Coombs Test Positive	36 (40%)	28 (57%)	0.05
Warm Antibodies (IgG)	70 (79%)	34 (69%)	0.18
Cold Antibodies (IgM)	19 (21%)	15 (31%)	0.23
Mixed Antibody Profile	5 (6%)	8 (16%)	0.04

Independent t-test used to compare mean between lab parameters

Chi-square test used for categorical variables;
P<0.005 indicate significant values;

Table 3 compared various treatment parameters between patients with idiopathic and secondary autoimmune hemolytic anemia (AIHA). The initiation of steroid therapy was high in both groups, with 89% of idiopathic AIHA patients and 86% of secondary AIHA patients receiving treatment, resulting in a p-value of 0.62, indicating no significant difference. However, the administration of intravenous immunoglobulin (IVIG) therapy was significantly more common in the secondary AIHA group (51%) compared to the idiopathic group (34%), with a p-value of 0.04. In contrast, rituximab was used significantly more often in patients with secondary AIHA (37%) than in those with idiopathic AIHA (11%), achieving a p-value of less than 0.01. Similarly, plasmapheresis was performed in 16% of secondary AIHA cases compared to only 3% of idiopathic cases, with a p-value of 0.01, highlighting a substantial difference in treatment approaches. Regarding transfusion requirements, 58% of idiopathic AIHA patients needed transfusions, while this figure was higher in secondary AIHA patients at 78%, with a statistically significant p-value of 0.02. The duration of steroid therapy was also significantly longer in the secondary AIHA group (45 days) compared to the idiopathic group (34 days), with a p-value of less than 0.01. Hospital stays were similarly prolonged for secondary AIHA patients (10 days) compared to idiopathic patients (7 days), with a p-value of less than 0.01, indicating a higher clinical burden in secondary cases. In terms of treatment response, a complete response was observed in 83% of idiopathic AIHA patients compared to 63% of secondary AIHA patients, with a p-value of 0.01, suggesting a better overall response in idiopathic cases. Partial responses were reported in 11% of idiopathic patients and 29% of secondary patients, although this difference was not statistically significant. Relapse occurrence was similar between groups, with 20% of

idiopathic and 24% of secondary patients experiencing a relapse, resulting in a p-value of 0.57, indicating no significant difference. Overall, these results suggest that while both groups receive steroid therapy at similar rates, secondary AIHA patients require more aggressive treatment strategies, including IVIG, rituximab, and plasmapheresis, and experience longer hospital stays and steroid therapy durations.

Table 3: Comparison of Treatment Parameters in Idiopathic versus Secondary AIHA (n=138)

Treatment Variables	Idiopathic AIHA Mean ± SD/N (%)	Secondary AIHA Mean ± SD/N (%)	p-value
Steroid Therapy Initiated	79 (89%)	42 (86%)	0.62
IVIG Therapy Administered	30 (34%)	25 (51%)	0.04
Rituximab Used	10 (11%)	18 (37%)	<0.01
Plasmapheresis Performed	3 (3%)	8 (16%)	0.01
Transfusion Requirement	52 (58%)	38 (78%)	0.02
Duration of Steroid Therapy (days)	34 ± 12	45 ± 18	<0.01
Hospital Stay (days)	7 ± 2	10 ± 3	<0.01
Response to Treatment Complete	74 (83%)	31 (63%)	0.01
Partial Improvement	10 (11%)	14 (29%)	
Relapse Occurrence	18 (20%)	12 (24%)	0.57

Independent t-test used to compare mean between lab parameters;

Chi-square test used for categorial variables;
P<0.005 indicate significant values;

DISCUSSION

The hematological condition known as Autoimmune Hemolytic Anemia (AIHA) is caused by decompensated acquired hemolysis, which is brought on by the host's immune system attacking self-red cell antigens. Autoantibodies, whether or not complement activation is present, are directed against erythrocytes [11]. In patients with idiopathic versus secondary Autoimmune Hemolytic Anemia (AIHA), this study sought to assess the clinical and laboratory features, therapeutic parameters, and response to therapy. The present findings offer important new information about patient demographics, test results, therapy modalities, and treatment outcomes. These details can be compared with previously published research to make relevant inferences [12]. The average age of 6.8 years for this study of 138 patients corroborates to previous studies reporting a predominance of AIHA in a paediatric population. Autoimmune disorders tend to have a slightly male bias, which is aligned with the majority of patients (58%) being male. The high prevalence of pallor (92%) and jaundice (78%) indicates severe hemolytic anemia symptoms among the patients. This aligns with the findings from (Voulgaridou and Kalfa et al., in 2021), stating

that young AIHA patients often present with symptoms like pallor and jaundice [13]. In the present study finding that the mean hemoglobin level of 7.1 g/dL confirmed the severity of anemia. The total bilirubin level of 3.8 mg/dL in this case, which is also shown to be classical in AIHA patients by (Gabelli *et al.*, in 2022) further represents the hemolytic process [14]. These results are important as they were for idiopathic AIHA which was the most prevalent type, to be precise 64% in idiopathic and 36% in secondary showed to have concordance. In the current study to found that laboratory parameters, including hemoglobin, total bilirubin and LDH levels were significantly different between idiopathic versus secondary AIHA. The hemoglobin level in idiopathic AIHA patients was higher than that in secondary patients (7.5 versus 6.9 g/dL), suggesting less pronounced anemia at the time of presentation among idiopathic cases [15]. Weli *et al.*, in 2020 previous study consistent with the observations by the secondary AIHA typically has a more severe clinical presentation and worse test values [16]. It is also possible that lower total bilirubin (3.6 mg/dL) in idiopathic AIHA than secondary AIHA (4.1 mg/dL) suggests less hemolysis among the former group. The results of the substantial difference in LDH level (620 U/L idiopathic versus 780 U/L secondary) between the two groups, which is further corroborating conclusions proposed by other authors, as LDH is involved in oxidizing redox reaction and, therefore an important marker of hemolysis severity [17]. Consistent with the findings of (Delesderrier *et al.*, in 2020) for secondary AIHA patients, the antibody profiles displayed a wider spectrum of reactivity, capturing underlying diseases. In fact, secondary AIHA had higher occurrence rates of mixed antibody profiles (16%) than idiopathic AIHA (6%) [18]. For treatment, initial steroid therapy was given to 89% of idiopathic and 86% secondary AIHA patients, denoting equivalence in commencing management. In contrast, there were significant differences in the use of complementary therapies. According to previous study that had a secondary AIHA, because of the association of such with other underlying disorders, usually needs a more intense therapy. The increased usage of IVIG (51% in secondary AIHA) and rituximab (37% in secondary AIHA) suggests a more aggressive therapy approach for secondary AIHA [19]. Moreover, the duration of steroid therapy was longer in secondary AIHA patients (45 days) than idiopathic patients (34 days), indicating a longer treatment course. These results are in line with the findings of previous study of (Dei *et al.*, in 2024) secondary cases usually stay in pellet longer than primary ones [19]. Treatment response 83% of idiopathic AIHA patients had a complete treatment response, 63% of the secondary AIHA patients had a complete treatment response. The contrast with treatment response emphasizes the generally favorable course of idiopathic case [20]. This aligns with the previous literature (Mueller *et al.*, 2018), supporting that initial therapy is often more effective in idiopathic AIHA than secondary variants which may have confounding factors influencing treatment outcomes [21]. This study indicated that laboratory results, treatment strategy and response to therapy differ significantly between idiopathic and secondary AIHA patients. The results are consistent with prior studies and support the importance of individualized management strategies based on AIHA pathogenesis. Further research is needed to provide long-term outcomes, quality of life and impact of new treatments in these patients.

CONCLUSIONS

In contrast to secondary AIHA patients who often required more intensive treatment including IVIG and rituximab, the idiopathic AIHA cases are less severe and respond better. These findings emphasized the need for accurate diagnosis and individualized treatment strategies tailored to each specific form of AIHA to ultimately improve patients' outcomes.

Authors Contribution

Conceptualization: KA
Methodology: BA, MAB, AK
Formal analysis: BA, FK
Writing, review and editing: UB, FK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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