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COVID-19-Induced Immune Dysregulation in Community-based Pediatric Autoimmune Hemolytic Anemia: Insights into Onset and Relapse Phases

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ABSTRACT

Autoimmune hemolytic anemia (AIHA) is a rare, but life-threatening hematologic condition in childhood. New evidence indicates that infection with SARS-CoV-2 can precipitate or worsen AIHA, yet systematic pediatric data are lacking.

OBJECTIVE: The study aims to explore the effect of COVID-19 on the onset of child AIHA relapse, report laboratory for differentiation and analyze statistical results. Methods: A retrospective cohort analysis was conducted of 40 children with AIHA. Eighteen of the cases had COVID-19 and 22 did not. Laboratory features, serology, inflammatory markera and relapse ratees were analyzed. Results: Hemoglobin levels were significantly higher, reticulocyte count was significantly higher, LDH level was significant higher, direct and total bilirubin levels were significantly lower and CRP and ESR levels checked before receiving transfusion had high rate of significance in cases of COVID-19–related AIHA when compared to non-COVID ($p < 0.04$). DAT positivity for both IgG and C3d was more common in the COVID group. The rates of relapse were 33% for the COVID-related group and 9% for the non-COVID group ($p > 0.04$). Conclusion: COVID-19 infection plays an important role in the development and recurrence of AIHA in children by increasing hemolysis and inflammation. Prompt identification of laboratory abnormalities and close follow-up may be life-saving.

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Introduction

In children, autoimmune hemolytic anemia (AIHA) is caused by autoantibodies that target antigens on the surface of red blood cells leading to their premature destruction [1]. It is usually divided into warm AIHA, with antibodies that are active at 37 °C (IgG mediated) and cold agglutinin disease, with IgM antibodies which bind complement at cooler temperatures [2]. Pediatric AIHA is rare, with a reported 0.2

per 100,000 children affected annually, but it has a high morbidity secondary to its acute presentation and the possibility of relapse [3,4]. Viral infections are among the well-known triggers inducing autoimmune cytopenias, such as Epstein-Barr virus, cytomegalovirus, parvovirus B19 and influenza [5,6]. The recent outbreak of coronavirus disease 2019 (COVID-19), which is due to SARS-CoV-2, has augmented the range of viral infections related to autoimmune complications [7]. There have been reports of immune-mediated cytopenias in the form of immune thrombocytopenia (ITP) and AIHA after COVID-19 infection in adults, as well as children [8–10]. Immunopathogenesis is believed to include multiple mechanisms. Molecular mimicry between viral antigens and red cell protein can lead to cross-reactive antibodies [11]. Hyperinflammatoty responses and cytokine storm can expose autoreactive clones and enhance complement activation [12].

COVID-19 has also been linked with multisystemic inflammatory syndrome in children (MIS-C), highlighting a susceptibility for dysregulation of the immune system among pediatric patients [13]. Despite multiple case reports, there are few systemic evaluations of COVID-19–associated AIHA in children. The majority of these publications are case reports or small series with no statistical comparison with a non–COVID-19 AIHA group [14–16]. The objective of this study was to compare blood indices including inflammatory and immunological markers, age between 3 and 7 years in children with AIHA (with COVID-19−associated AIHA vs non–COVID-19− associated AIHA)Moderators Purpura Management M1.

Methods

A retrospective cohort analysis was performed Community-based pediatric patients. Forty (age, 3–7 years) children diagnosed as AIHA based on confirmed evidence were recruited. Classification: COVID-associated AIHA (n=18): onset or relapse in a period of 6 weeks since SARS-CoV-2 was confirmed (RT-PCR or serology); Non-COVID AIHA (n=22): cases without temporal relation to SARS-CoV-2. Inclusion criteria confirmed diagnosis of AIHA with positive DAT and full laboratory and clinical information was available. The exclusion criteria were as follows: congenital hemolytic anemias (glucose-6-phosphate dehydrogenase [G6PD] deficiency, hereditary spherocytosis) and primary immunodeficiencies. Laboratory findings: Hb, reticulocyte % and value (ret), LDH, indirect bilirubin, haptoglobin level, DAT profile (IgG and C3d), titer of cold agglutinin test (CAT) and thermal amplitude; CRP, ESR levels; serum immunoglobulin level IgG, IgM,IgA. Statistical analysis: Continuous data were compared by the Student's t-test or Mann–Whitney U test and categorical data using chi-square tests or Fisher's exact test. Association between COVID-19 and re-lapse risk was estimated by logistic regression, adjusting for baseline hemolysis markers, as well as DAT pattern. Results with p-value <0.05 were considered statistically significant.

Results and Discussion

Of these, 40 children Community-based (18 COVID-related, 22 non-COVID) and baseline demographics were similar with no statistically significant difference in the age and sex distribution. Hematology: The mean hemoglobin was statistically significantly lower in COVID associated AIHA (6.8 ± 1.1 g/dL) when compared with the non COVID cases (7.6.± 1.2, p=0.04). The reticulocyte percentage was greater in cases of COVID (9.8% vs 7.4%; P = 0.03). Hemolysis indices: LDHemia was significantly higher in the COVID patients (785 ± 180 vs. 610 ± 150 U/L, $p<0.01$). In addition, indirect bilirubin was significantly higher (2.8 ± 0.9 vs 1.9 ± 0.7 mg/dL; $p<0.01$). Haptoglobin was also lower in COVID cases, but with no statistical significance (14 vs 19 mg/dL, p=0.09). Immunology: DAT tested positive for IgG/C3d in 83% of COVID cases compared with 73% in non-COVID. Cold agglutinins were elevated in limited number of patients. ‘Inflammatory markers’: CRP (34 versus 18 mg/L; $p<0.01$) and ESR (52 versus 27 mm/h; $p<0.01$) were significantly higher in COVID-associated cases. Relapse: Recurrence occurred within 6-moth of remission in 33% COVID AIHA and in 9% non-COVID cases (p=0.03). COVID-19 was validated as independent predictor for relapse by logistic regression (OR, ∼3.5 [95% CI: 1.2–11.0]). These results indicate that patients with pediatric AIHA and SARS-CoV-2 infection may exacerbate the

severity of hemolysis as well as increase the risk for recurrence, which is consistent with what previously reported [17–22].

Tables

Table 1. Baseline characteristics of children with AIHA (age 3–7 years)

Variable	COVID-associated AIHA (n=18)	Non-COVID AIHA (n=22)	p-value
Age (years)	5.1 ± 1.3	5.3 ± 1.2	0.42
Sex (M/F)	10/8	11/11	0.71
New onset / Relapse	12 / 6	14 / 8	0.65

Table 2. Hemolysis markers at presentation

Variable	COVID-associated AIHA (n=18)	Non-COVID AIHA (n=22)	p-value
Hemoglobin (g/dL)	6.8 ± 1.1	7.6 ± 1.2	0.04*
Reticulocytes (%)	9.8 ± 2.5	7.4 ± 2.1	0.03*
LDH (U/L)	785 ± 180	610 ± 150	<0.01*
Indirect Bilirubin (mg/dL)	2.8 ± 0.9	1.9 ± 0.7	<0.01*
Haptoglobin (mg/dL)	14 ± 6	19 ± 7	0.09

Table 3. Immunohematology and inflammatory markers

Variable	COVID-associated AIHA (n=18)	Non-COVID AIHA (n=22)	p-value
DAT IgG positivity	15 (83%)	16 (73%)	0.42
DAT C3d positivity	14 (78%)	20 (91%)	0.18
Warm AIHA (%)	78%	59%	0.12
Cold AIHA (%)	11%	23%	0.20
CRP (mg/L)	34 ± 10	18 ± 6	<0.01*
ESR (mm/h)	52 ± 14	27 ± 10	<0.01*
Serum IgG elevation (%)	22%	14%	0.47

Table 4. Relapse within 6 months

Variable	COVID-associated AIHA (n=18)	Non-COVID AIHA (n=22)	p-value
Relapse (%)	33%	9%	0.03*
Median time to relapse (days)	74 (IQR 62–96)	88 (IQR 70–110)	0.21

Conclusion

The clinical and laboratory profile of Community-based AIHA in the age group 3–7 years is significantly affected by COVID-19 infection. It correlates with lower levels of hemoglobin, higher count of reticulocytes, raised hemolysis markers and inflammatory indices as well as higher relapses. Strict

vigilance and an early identification of the labicular changes may be crucial for a better outcome in this frail population.

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