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Case Series

Paediatrics Section

Autoimmune Haemolytic Anaemia-A Spectrum of Presentation in Children

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ABSTRACT

Autoimmune Haemolytic Anaemias (AIHAs) are rare in children. They can be either a primary disease or secondary to/triggered by a host of other clinical conditions. We present five interesting cases of paediatric AIHA associated with infections (viral, bacterial and atypical) and autoimmune diseases {Systemic Lupus Erythematosus (SLE) and Autoimmune Hepatitis (AIH)}. The H1N1 influenza associated AIHA responded to oseltamivir and Intravenous Immunoglobulin (IvIg) while the cases secondary to *Mycoplasma pneumoniae* and pneumococcal bacteraemia required only treatment of the primary infection. AIHA with SLE responded well to corticosteroid therapy but the patient with AIH and AIHA succumbed to severe liver failure. Rest of the four cases with good response to therapy did not have any recurrence/relapse of AIHA during their follow up periods.

Keywords: Autoimmune hemolysis, Autoimmune hepatitis, *Mycoplasma pneumoniae*, Systemic lupus erythematosus

AIHAs are rare in children with an estimated incidence of 0.2 per million individuals below 20 years of age [1]. Peak incidence is found in less than four years of age [2]. Pathologically, AIHAs are classified on the basis of the thermal range of the pathogenic antibody (warm antibody AIHA and cold antibody AIHA) and, whether it is associated with another disease or not (primary or secondary). Clinically, two predominant types of AIHAs are recognized in children- an acute transient form that is more common in infants and younger children and a chronic, refractory type, typically seen in older age group. The former are usually primary cold antibody AIHAs and the latter are either warm or secondary AIHAs [3].

We encountered five interesting cases of paediatric AIHA at a tertiary care paediatric center in Northern India [Table/Fig-1]. AIHA was diagnosed in the presence of anaemia, evidence of hemolysis on peripheral smear, elevated reticulocyte count corrected for the degree of anaemia, elevated unconjugated bilirubin, positive direct Coomb's test and elevated Lactate Dehydrogenase (LDH) levels [1]. Facilities for further characterization of auto antibodies were not available. Depending on the history, clinical presentation and associated features, other investigations were performed. In addition, Toxoplasmosis, Rubella, Cytomegalovirus and Herpes simplex infections (TORCH) screening was done for the infants. A detailed drug history was taken in all to exclude drug induced AIHA. All the children were given iron and folic acid in addition to specific therapies. They were followed weekly during first month, fortnightly during next month and then monthly for the next four months.

CASE SERIES

The first patient was an infant presenting with influenza like illness followed by tachypnoea and pallor. Examination was remarkable with splenohepatomegaly and dysmorphism suggestive of Turner's syndrome. Investigations confirmed H1N1 infection {positive Polymerase Chain Reaction (PCR) from nasal swab} but her karyotype was normal. The child's infection was managed with oseltamivir and IvIg in addition to supportive care. She did not require corticosteroids and during follow up for next three months, her haemoglobin level normalized.

The second child had clinical features suggestive of rheumatological disease apart from AIHA. Investigations {Positive Antinuclear Antibody (ANA), antibody against double stranded DNA and anticardiolipin antibody} confirmed the diagnosis of Systemic Lupus Erythematosus (SLE) without any renal involvement. She was started on induction therapy with corticosteroids (Prednisolone@2 mg/kg/day) with rapid resolution of anaemia. Presently, on maintenance therapy with azathioprine, her disease is under remission and haemoglobin level has normalized with no recurrence of haemolysis.

The third patient had a subacute onset of non severe respiratory illness along with extrapulmonary manifestation in the form of anaemia, jaundice and erythema nodosum prompting an atypical infection. The diagnosis of *Mycoplasma pneumoniae* infection was confirmed by multiplex PCR and the child was treated by azithromycin alone with resolution of anaemia over next four weeks.

The fourth case presented as acute abdomen. Ultrasound (US) showed mild ascites with echogenic fluid. Blood and ascitic fluid culture grew *Streptococcus pneumoniae*. The child recovered with antibiotic therapy and supportive care without any need for immunomodulatory agents. On follow up for eight months, he was asymptomatic and his haematological parameters were also stable.

The fifth case had conjugated hyperbilirubinaemia, hepatosplenomegaly and history of recurrent episodes of jaundice with fever during last six months. After ruling out viral causes of hepatitis, an autoimmune etiology could be established {positive ANA and anti Liver Kidney Microsome (LKM) 1 antibody}. She developed hepatic encephalopathy and died. Post mortem histopathology of liver further confirmed the diagnosis of AIHA [Table/Fig-1].

DISCUSSION

We describe five paediatric cases of secondary AIHA with different associations/triggers. The first case was associated with H1N1 infection. Both influenza virus infection and influenza vaccine have been reported to trigger AIHA and Evan's syndrome in children and adults [4]. The reported cases of AIHA associated with influenza mostly had worse outcome inspite of steroid therapy, this prompted us to treat the infant in our case with IvIg. Also subsequent corticosteroid therapy was not required in our case. But use of IvIg in AIHA induced by influenza and other viral infection needs to studied in larger prospective cohorts before its use can be recommended in such settings.

AIHA though rare in SLE, is found more commonly in the childhood form of the disease than in adults [5]. Both American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC) recognise AIHA as one of the diagnostic criteria for SLE. AIHA may be the first manifestation of SLE and can appear several years before the diagnosis of SLE is made [6]. Presence of ACA has also been associated with AIHA in SLE. In the absence of any established protocol of therapy, we chose to treat the patient with corticosteroid as, it would help in both the conditions.

Almost in 25% of cases of *Mycoplasma pneumoniae* infection can have extrapulmonary manifestations before, during, after, or in the absence of pulmonary signs. Formation of cold agglutinins is

Age/ Gender	1 year/F	8 years/F	6 years/M	2 years /M	10 years/F
Presenting Complaints	High grade fever along with cough for 5 days, Pallor for 3 days, fast breathing for 2 days	Pallor for 7 days, fatigue for 7 days, jaundice for 3 days,	Low grade fever along with cough for 7 days, Pallor for 5 days, Jaundice for 3 days	Fever for 5 days, pain abdomen for 3 days and vomiting for 2days	High grade fever for 3 days, pallor & jaundice for 2 days
Other Significant History	Loose stools for 3 days.	Photosensitive rash over face for 1 month, pain and swelling of B/L knee joint off and on for 1 month	Rash over body for 3 days	Nil	Fever & jaundice twice during last 6 months
Icterus	+	+	+	+	++
Lymphadenopathy	-	-	-	-	-
Organomegaly	Spleen +, hepatomegaly +	Spleen +	Spleen +	Spleen +, hepatomegaly +	Spleen +, hepatomegaly +
Other Significant Examination Findings	Tachypnoea but no chest retraction or hypoxemia; dysmorphism (low set ears, low hairline, high arched palate, short fingers and toes)	Malar rash; B/L knee joint mild effusion but no other signs of inflammation	Erythema nodosum like rash; no respiratory distress; chest examination within normal limits	Sick looking; severe generalized abdominal tenderness and mild ascites	Nil
Hemogram (Hb; TLC; plt; DLC)	7.2/16700 /3.12/ N63 L27M6E4	6.0/14800 /1.5/N67 L29M3E1	6.6/19340 /4.23/ N71L23 M4E2	7.6/38 600/2.10/ N83 L16M1E0	5.8/ 210 00/2 .31/ N 76L 14M 3E7
Corrected Reticulocyte Count	5.6%	3.8%	4.4%	5%	3.8%
Total Bilirubin/ Conjugated (mg/dl)	3.2/ 0.5	4.8/0.8	4.5/0.6	3.8/0.6	6.2/3.8
LDH (U/L)	1231	667	585	1543	548

[Table/Fig-1]: Description of five cases of AIHA.

frequently observed during *Mycoplasma pneumoniae* infections and these may lead to hemolysis in up to 10% of patients. *Mycoplasma pneumoniae* associated AIHA is known to respond well to macrolides alone, seldom requiring immunosuppressive therapies [7] and the same was also seen in our case.

Bacon et al., also describes a patient similar to our fourth case with pneumococcal bacteraemia and AIHA which improved without any immunomodulatory agents. They hypothesize that effective control of infection may diminish the activating signals to the plasma cells that produced anti-red cell antibody, thereby terminating the autoimmune process [8].

AIH and AIHA has been reported sparingly in literature [9]. Though Hepatitis B and Hepatitis C infected patients are known to manifest with a multitude of autoimmune phenomena, our fifth patient did not have any such infection. Though, high dose intravenous corticosteroid therapy was started in the child, she succumbed to severe hepatic failure.

Though, a study had found prolonged onset of symptoms, increased reticulocyte count, increased numbers of nucleated RBC and early WBC precursors and decreased platelet count to be associated with poor outcome [10], another study from India refuted this [11]. Four of our five patients also had a very good response to specific therapy with or without immunosuppression.

CONCLUSION

AIHA may present in association with a spectrum of clinical conditions ranging from infections (viral, bacterial and atypical) to autoimmune disorders. Early identification coupled with specific therapy with or without immunosuppressive therapy is associated with a fairly good outcome even in secondary AIHA in children.

ABBREVIATIONS

Hb-Haemoglobin; TLC-Total Leucocyte Count; DLC-Differential Leucocyte Count; N-Neutrophil; L-Lymphocyte; E-Eosinophil; M-Monocyte, B-Basophil; Plt-Platelet Count; LDH-Lactate Dehydrogenase.

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