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RESEARCH ARTICLE

CLINICOETIOLOGICAL STUDY OF HEMOLYTIC ANAEMIA IN CHILDREN PRESENTING TO A TERTIARY CARE HOSPITAL OFKASHMIR

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Abstract

Anemia is said to be present when the hemoglobin levels are more than two standard deviations below the mean for the child's age and sex. Hemolytic anemias arise when red blood cells have decreased survival either due to an intrinsic abnormality of the cell or due to extrinsic factors or both. Hemolytic anemias constitute important cause of mortality and morbidity in developing countries. These group of anemias have various clinical presentations starting from their age of onset of symptoms, failure to thrive, anemia, jaundice, splenomegaly, cholelithiasis, cardiomegaly, congestive cardiac failure, severe life-threatening infections and chronic disabilities leading to distress in the families. The present study attempts to reveal the clinical and etiological profile of patients with different types of hemolytic anemia admitted in a pediatric tertiary care hospital of Kashmir. Review of literature shows only few epidemiological studies particularly in this part of the country, and no such study in our state though the disease is fairly prevalent. We undertook this study with this idea.

Aims and Objectives: The aims and objectives of this study was to determine clinical and etiological profile of hemolytic anemia in children aged 1month to 18 years admitted in tertiary care hospital of Kashmir.

Materiaals & Methods: This prospective observational study was carried out in a pediatric tertiary care hospital in Kashmir over a period of two years. Prior to initiation of study, ethical clearance was obtained. All patients admitted in the indoor of department of pediatrics between age group of 1 month to 18 years with evidence of hemolysis were included in the study. 50 cases were included in the study after obtaining written informed consent from parent or guardian. A detailed history, examination and required investigations were collected. Data was entered and assessed in MS Excel.

Results: The study was based on 50 patients, almost equal males and females, 1month to 18 years of age. The most common hemolytic anemia was beta thalassemia major (n=17, 34%), followed by autoimmune hemolytic anemia(n=10,20%), hereditary spherocytosis (n=5,10%), thalassemia trait (8%), pyruvate kinase deficiency (8%) and glucose 6 phosphate dehydrogenase (8%), thalassemia intermedia (4%), sickle cell trait (2%), microangiopathic hemolytic anemia (2%), hereditary xerosis (2%) and hereditary stomatocytosis (2%). Highest

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number of the cases was less than 3 years old (56%). The most common clinical presentation was jaundice, which was present in all cases, followed by splenomegaly (60%), hepatomegaly (30%), hemolytic facies (26%). Splenomegaly was seen in all cases of thalassemia major, thalassemia intermedia, beta thalassemia trait, hereditary spherocytosis, 2 cases of pyruvate kinase deficiency and 3 cases of glucose 6 phosphate dehydrogenase deficiency. Spleen >5cm was seen in 10 patients. Massive splenomegaly with abdominal discomfort was seen in 3 cases. The mean hemoglobin was least in beta thalassemia major followed by beta thalassemia intermedia, Hereditary spherocytosis, autoimmune hemolytic anemia, glucose 6 phosphate dehydrogenase deficiency and the highest mean hemoglobin was seen in pyruvate kinase deficiency. Means for serum ferritin and serum bilirubin were calculated.

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Introduction:-

Anemia is said to be present when the hemoglobin levels is more than two standard deviations below the mean for the child's age and sex. [1] According to world health organization, anemia is defined as when hemoglobin levels are below following levels. [2]

Age Group	Hemoglobin
06 months to 06 years	< 11 gm/ dl
06 years to 18 years	< 12 gm/ dl

Hemolytic anemias are a group of conditions characterized by an excessive breakdown of red blood cells. Hemolytic anemias arise when red blood cells have decreased survival either due to an intrinsic abnormality of the cell or due to extrinsic factors or both. Hemolysis is caused either by abnormalities in red blood cells themselves (in Hemoglobin), the red blood cell membrane or intracellular enzymes known as corpuscular anemia or by external causes (immune mediated or mechanical damage) known as extra corpuscular anemia.These group of anemias have various clinical presentations starting from their age of onset of symptoms, failure to thrive, anemia, jaundice, splenomegaly, cholelithiasis, cardiomegaly, congestive cardiac failure, severe life-threatening infections and chronic disabilities leading to distress in the families.

There are numerous causes of hemolytic anemia, which have several ways that can be broken down to include acute and chronic disease, immune vs. non-immune mediated, intravascular or extravascular, inherited or acquired, and intracorpuscular or extracorpuscular.

Intracorpuscular causes refer to abnormalities in the red blood cell itself. A red blood cell can be internally damaged when the solubility of hemoglobin is altered (hemoglobinopathy, e.g., sickle cell disease, thalassemias), the structure of the membrane or cytoskeleton is changed (membranopathy, e.g., hereditary spherocytosis, hereditary elliptocytosis), or, its metabolic abilities are decreased (enzymopathy, e.g., glucose-6-phosphate deficiency, pyruvate kinase deficiency). Alternatively, extracorpuscular causes refer to defects that were influenced by external factors, including mechanical, immune-mediated, or infectious.

The World Health Organization (WHO) has suggested that about 5% of the world population are carriers for different inherited disorders of hemoglobin[3] WHO reports also state that about 370,000 severely affected homozygotes or compound heterozygotes of thalassemia are born every year. The UNICEF in 1996 estimated that there were 29.7 million carriers of beta thalassemia trait in India and about 10,000 infants with homozygous beta thalassemia born every year [4]. The general incidence of thalassemia trait and sickle cell hemoglobinopathies in India varies between 3-17% and 1-44% respectively [5,6,7]. It is estimated that there are about 65,000-67,000 beta-thalassemia patients in India with around 9,000- 10,000 cases being added every year. The carrier rate for beta-thalassemia gene varies from 1 to 3% in Southern India to 3 to 15% in Northern India[8,9,10]. In developing countries, in which there is high mortality from infections and malnutrition in the first year of life, many of the hemoglobinopathies are unrecognized. Sickle cell anemia and thalassemia major can cause life-threatening situation

and chronic ill-health. They pose economical and psychological burden on the affected individual and his/her family, and the society as a whole. Hence, the population needs to be screened for hemoglobin.

Classifications of hemolytic anemia		
TYPE	DEFINITION	CAUSES
(A) BY RBC PATHOLOGY		
1) Intrinsic type	Increased destruction of RBCs due to a defect within the RBCs	-Erythrocyte membrane defects: Hereditaryspherocytosis, paroxysmal nocturnalhemoglobinuria (PNH) -Enzyme defects: glucose- 6- -phosphatedehydrogenase deficiency (G6PD deficiency), pyruvate kinase deficiency(PKD) -Hemoglobinopathies: sickle cell disease,thalassemia, hemoglobin C disease
2) Extrinsic type	Abnormal breakdown of normal RBCs	-Mechanical destruction in large vessels: e.g., prosthetic heart valves -Shearing of RBCs due to occlusion of small vessels microthrombi: e.g., hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) Immune reactions due to infections (e.g., Mycoplasma) or tumors (e. g. chronic lymphocytic leukemia), Infections causing increased destruction of RBCS (e. g. Babesia, malaria, Bartonellabacilliformis), Isoimmune reactions: e.£., ABO/Rh Incompatibility, Autoimmune reactions: e.g., autoimmune HA (AHA) Increaseddegradation by the spleen (hypersplenism)
B) BY SITE OF RBC BREAKDOWN		
1) Intravascular type	Increased destruction of RBCs within the vessels	-Toxins (e.g., snake bites) and oxidizing agents (e. g, copper poisoning, G6PD deficiency) -Immune-mediated anemia (PNH, transfusion ABO incompatibility, hemolytic anemia of the newborn, cold agglutinin disease) -Macroangiopathic anemia (mechanical destruction by, e.g., prosthetic cardiac valves) -Microangiopathic anemia (e.g., TTP, HUS, disseminated intravascular coagulation, HELLP syndrome, systemic lupus erythematosus)
2) Extravascular type	Increased destruction of RBCs in the reticuloendothelial system, primarily spleen	-RBC defects (e.g., sickle cell disease, spherocytosis, pyruvate kinase deficiency) - Immune-mediated anemia (warm and cold agglutinin disease PNH).

Aims and Objectives:-

The aims and objectives of this study were to determine clinical and etiological profile of hemolytic anemia in children aged 1month to 18 years admitted in tertiary care hospital of Jammu and Kashmir.

Materiaals & Methods:-

This prospective observational study was carried out in a pediatric tertiary care hospital in Kashmir over a period of two years from October 2020 to October 2022.

Ethical Issues:

Ethical clearance from the ethical committee of the institution; and, consent from the patient's parents/ legal guardians.

Subjects:

All patients admitted to the inpatient department of pediatrics, GMC Srinagar, between age group of 1 month to 18 years with evidence of hemolysis were included in the study

Inclusion Criteria:

1.Children with age group 1month to 18 years

2. Children presenting with laboratory diagnosis of Anemia and Absolute Reticulocyte Count (ARC) >1.5lac.
Exclusion criteria:
Neonates to rule out Rh mediated hemolytic anemia.

Methods Of Data Collection:-

A) History: information about age ,gender ,consanguinity; history of gum bleeding, weight loss, bony pains, recurrent infections, persistent fever and petechiae, dark colored urine, rashes, leg ulcers; detailed family history of severe anemia and/ or need of multiple blood transfusions, young –age gallstones/ cholecystectomy , recurrent jaundice, hydrops, neonatal jaundice; history of travel to endemic areas, any chronic illness; any recent drug intake or of development of anemia following exposure to certain drugs and foods.
B) Examination: Thorough physical examination with specific focus on signs of anemia, jaundice, splenomegaly, hepatomegaly, and hemolytic facies,petechia,lymphadenopathy, any skeletal anomalies or skin pigmentation.
C) Laboratory investigations: Complete blood count (by Sysmex automated cell counter), reticulocytecount (brilliant crystal stain) and peripheral blood film (Leishman's stain),DCT, ICT, LDHand serum uric acid level was done in all cases. Other biochemical and radiological investigations were carried out on need basis.

Observations and Results:-

The study included a total of 50 patients who fulfilled the inclusion criteria, out of which 26(52%) were males & 24(48%) were female. The most common hemolytic anemia was beta thalassemia major (n=17, 34%), followed by autoimmune hemolytic anemia(n=10,20%), hereditary spherocytosis (n=5,10%), thalassemiatrait (8%), pyruvate kinase deficiency (8%) and glucose 6 phosphate dehydrogenase (8%), thalassemia intermedia (4%), sickle cell trait (2%), microangiopathic hemolytic anemia (2%), hereditary xerosis (2%) and hereditary stomatocytosis (2%). All patients of G6PD deficiency and most patients of hereditary spherocytosis were males. Gender wise distribution was similar in other etiological groups. A positive family history was documented in 22% of the cases, of which 10% suffered from beta thalassemia major. Highest number of the cases was less than 3 years old (56%), followed by the age group of 4-6 years(26%).

The most common clinical presentation was jaundice, which was present in all cases, followed by splenomegaly (60%), hepatomegaly (30%), hemolytic facies (26%),cardiac manifestations(24%),growth retardation and gallstones. Splenomegaly was seen in all cases of thalassemia major, thalassemia intermedia, beta thalassemia trait,hereditary spherocytosis, 2 cases of pyruvate kinase deficiency and 3 cases of glucose 6 phosphate dehydrogenase deficiency. Spleen >5cm was seen in 10 patients. Massive splenomegaly with abdominal discomfort was seen in 3 cases. Splenectomy was undertaken in 3 patients & cholecystectomy in one patient of hereditary spherocytosis. Hemolytic facies were noted in 11 cases of thalassemia major & 2 cases of thalassemia intermedia. Growth retardation was seen in ten patients of beta thalassemia major,of these seven in the age group between 1month-3 years,three in age group of 4-6 years. Height less- than- 3rd percentile was seen in 5 patients of beta thalassemia major (3 were in the age group of up to3years, and 2were 4-6 years). X ray skull showed crew cut appearance in 2 patients of beta thalassemia major. All but three children received routine immunization.

The mean hemoglobin was least in beta thalassemia major followed by beta thalassemia intermedia, Hereditary spherocytosis, autoimmune hemolytic anemia, glucose 6 phosphate dehydrogenase deficiency and the highest mean hemoglobin was seen in pyruvate kinase deficiency. 75% cases presented with hemoglobin in the range of 5-8gm/dl, 19% presented with hemoglobin less than 5gm/dl and 6% presented with hemoglobin in the range more than 8gm/dl. From the available biochemical parameters, the respective means of serum ferritin and serum bilirubin values were calculatedwith highest mean serum ferritin observed in beta thalassemia major (1400ng/dl) followed by thalassemia intermedia(950ng/dl) and thalassemia minor(610ng/dl). The highest total serum bilirubin was observed in beta thalassemia major (3.1mg/dl), followed by thalassemia intermedia(2.9g/dl), by G6PD deficiency (2.8g/dl). The fetal hemoglobin values were found to be raised in thalassemia major, thalassemia intermedia and thalassemia minor.

Discussion:-

Our study was a prospective observational study, conducted at postgraduate department of pediatrics, an associated tertiary care hospital of Government Medical College-Srinagar, from October 2020 to October 2022. It included 50 patients, out of which 26 were males and 24 were females.The commonest congenital hemolytic anemia was Beta thalassemia(34%),followed by hereditary spherocytosis (10%). The most common acquired hemolytic anemia was autoimmune hemolytic anemia(10%). The World Health Organization has suggested that about 5% of the world's

population is carriers for different inherited disorders of hemoglobin[11]. WHO reports also state that about 370,000 severely affected homozygotes or compound heterozygotes of thalassemia are born every year. The UNICEF, in 1996, estimated that there were 29.7 million carriers of beta thalassemia trait in India and about 10,000 infants with homozygous beta thalassemia born every year[12]. Beta thalassemia major accounted for 34% of cases with Mean Hb, absolute reticulocyte count and HbF 4.5g/dl 2.0 and 70% respectively.Thalassemia is not common in Kashmir. Out of the 17 children of beta thalassemia major, four hailed from Kolkata and two from Haryana, whose parents are working here. Five patients hailed from Poonch and Rajouri districts of Jammu region. Hb-electrophoresis revealed mean HbF of 70%. Serum bilirubin was elevated in all cases with a mean of 2.8g/dl. Nine out of seventeenpatientsreceived frequent blood transfusions (15-20) in a year. The goal was to keep hemoglobin between 10g/dl and 13-14 g/dl. About 80 % patients had developed iron overload with mean serum iron and mean serum ferritin as 790 mcg/dl and 1400mcg/dl, respectively. All these patients received chelation therapy, oral deferasirox 20-30mg/kg/day. Two cases wereon thyroid replacement therapy. Their thyroid profiles were under control.

Four patients in this study were diagnosed as beta thalassemia trait. Their age ranged from 3-5 years with jaundice as their most common complain. Hemoglobin ranged from 6-10gm/dL, hematocrit: 16- 25%, MCV: 54-73µm3, MCH: 15-32pg, MCHC: 28-34gm/dL, Mean Reticulocyte count 3.5 & mean serum bilirubin 1.6g/dl. These patients infrequently required blood transfusions. There were 2 cases of thalassemia intermedia, both products of 3rd degree consanguineous marriages. They required transfusions 5-6 times in 6 months. These patients had mean hemoglobin, retic count and mean HbF of 5.0 gm/dl, 6.0 and 48%. One of thesepatientshailed from Poonch area of Jammu region. Both the patients were started on chelation therapy and bore no evidence of iron overload or organ dysfunction.

One case of Sickle cell trait was admitted with hemoglobin of 6.5g/dl,MCV of 84,no sickle cells seen on the peripheral blood film. Clinical manifestations were mild,requiring occasional blood transfusions. No crisis was seen. This child hailed from Uttar Pradesh, whose parents worked here in a factory. Hb-electrophoresis confirmed the diagnosis.

Four cases of Glucose 6 phosphate dehydrogenase deficiency were diagnosed with ages 5-10 years. Historyof fava beans intake was present in one patient, positive family history in three patients. All patients were male. Avoidance of certain drugs and foods in these patients was been emphasized. All the patients were vaccinated against hepatitis A and B. Evidence from the studies indicates that neonatal screening programs are vital to manage the public health burden of G6PD in a population. Neonatal screening programs for the condition have the potential to increase parental and caretaker awareness, thereby facilitating early access to treatment, with resultant diminished mortality and morbidity [13,14,15,16].

Four patients were diagnosed as cases of Pyruvate kinase deficiency. Two of these, presented with severe anemia,with mean Hb of 7.6 gm/dL. All patients had splenomegaly with one having massive splenomegaly and cholelithiasis. This patient underwentboth splenectomy and cholecystectomy. All these patients required transfusion every two months.

Five cases were identified as hereditary spherocytosis with ages of 6 months -13 years. All patients had jaundice,progressive pallor with mild to moderate splenomegaly. Osmotic fragility test was positive in all these patients. Hereditary spherocytosis is common in Kashmir. These patients required transfusions every 2 months. One case of microangiopathic hemolytic anemia was identified, a 2-year-old child who presented with atypical hemolytic uremic syndrome. She was treated conservatively with iv fluids, salt restriction, fresh frozen plasma,packed red blood cells and pulse therapy of methylprednisolone and was discharged after 2 weeks of hospitalization. One case of hereditary stomatocytosis,second only to previously detected case in the department of hematology, SKIMS, was recognized. She presented with severe anemia, jaundice and mild splenomegaly. Complete blood count showed Hemoglobin of 6.8g/dl, with raised MCV, decreased MCH with stomatocytes on peripheral blood typical of hereditary stomatocytosis. Family history was insignificant. Symptoms related to anemia and jaundice were mild so that no therapy was required. One case of hereditary xerocytosis, an8-year-old female child with jaundice,severe anemia and moderate splenomegaly with multiple transfusions in the past, was identified. Patient had been misdiagnosed as hereditary spherocytosis previously. Complete blood count showed raised MCH and decreased MCV. Peripheral blood film showed xerocytes with spherocytes suggestive of hereditary xerocytosis. The clinical phenotype was mild with mild iron overload and splenomegaly requiring infrequent transfusions.

Ten patients were diagnosed as Autoimmune hemolytic anemia. Dyspnea, easy fatigability, and hepatosplenomegaly were the most common presenting features. Mycoplasma pneumoniae was the leading cause of secondary autoimmune hemolytic anemia. Out of the 10 patients, more than 60% had severe anemia requiring multiple blood transfusions. Five patients improved on corticosteroid therapy (pulse therapy followed by oral steroids for 2 weeks with tapering over 4 weeks). Three patients got better withimmunosuppressants along with steroids. One patient improved spontaneously and did not receive any drug. All these patients are on regular follow up. One patient, with secondary autoimmune hemolytic anemia and underlying Hodgkin lymphoma, died due to fulminant fungal sepsis and hemophagocytosis in the pediatric ICU. Most of these patients had splenomegaly. Treatment duration was longer for secondary autoimmune hemolytic anemia than primary. Autoimmune hemolytic anemia has good prognosis if diagnosed early. Direct Coomb's test is indicated in patients with anemia, indirect hyperbilirubinemia and abnormal peripheral smear, especially in females. Autoimmune hemolytic anemia may be the first manifestation of underlying disease which is treatable.

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