2) Anemias II - Dr. Hersh

Sideroblastic Anemia (Iron loading anemia)

- It's a rare hereditary hypochromic anemia, in which there are: excessive iron stores, high serum iron, decreased iron binding capacity & an exceptional ability to accumulate iron from the diet at a rapid rate.
- It is a form of disturbance of heme biosynthesis, in which iron is not utilized for blood formation, but is deposited, in different tissues.
- Bone marrow shows numerous sideroblasts which are iron- granule containing normoblasts.
- Anemia may start from early childhood. Hepato-splenomegaly may be present.
- Treatment: measures such as; blood transfusions, iron chelating agents & rarely splenectomy may help.

Megaloblastic Anemia

- A rare form of anemia in children, caused by deficiency of vitamin B12 (cyanocobalamin) & or folic acid.
- Children fed by goat’s milk are potentially at risk of folic acid deficiency. Other causes of megaloblastic anemia in children includes: phenytoin anticonvulsants, folic acid antagonists as methotrexate, and chronic hemolytic anemia (due to increased demands),
- Infestation by fish tape worm (Diphylobothrium latum) causes B12 deficiency.
- Both steatorrhea & chronic liver disease cause deficiency of both B12 & folic acid.
- In addition to these deficiencies M. A. is a particularly common form of anemia in children with protein calorie malnutrition.
- M. A. is characterized by the presence of macrocytic red cells with or without leucopenia, thrombocytopenia & hypersegmented neutrophils in the peripheral blood & predominance of megaloblasts with erythroid hyperplasia in the bone marrow.
- Serum B12 & or F. A. is low.
- Treatment: I.M. B-12; initially daily 15 – 30 microgram & then once every 2 – 4 weeks until complete recovery achieved. Lifelong treatment is required in the hereditary (A. R.) or autoimmune forms. When folic acid is required, it is given in a dose of 10 – 30 mg / day for few weeks.

Hemolytic Anemias (H. A.)

- H. A. is characterized by increased R. C. destruction.
- Normally about 1% of R.C.s are destroyed & removed from the circulation each day.
- The bone marrow however, has the capacity to increase its production of R. Cs. up to 8 times.
- H. A. develops when the rate of R. C. destruction exceeds the ability of the marrow to compensate & produce new R. Cs.

Etiologic classification of H. A.

A. Intracorpuscular defects; all of these generally speaking are of hereditary type & include:
   1. R. C. membrane disorder as spherocytosis & ovalocytosis (elliptocytosis).
   2. R. C. enzyme deficiencies: G6PD, pyrovate kinase deficiency.
   3. Ineffective erythropoiesis as thalassemia.
   4. Hemoglobinopathies as sickle cell disease & Hb C, D. E disease.
   5. Paroxysmal Nocturnal hemoglobinuria.

B. Extra corpuscular defects: generally causes of this group are acquired & include:
   1. Immune hemolytic anemia:
      i. Isoimmune, as Rh & ABO hemolytic disease.
      ii. Autoimmune.
   2. Nonimmune hemolytic anemia:
      i. As occurs in severe burns, prosthetic heart valves, bacterial sepsis, malaria, venom & metallic poisoning as lead & copper.
General clinical & laboratory evidences of H.A.:

A. Clinical:
1. Anemia: pallor, breathlessness on exertion, palpitation, fainting, headache.
2. Jaundice, usually mild & fluctuates. Absence of jaundice does not exclude H. A.
3. Dark urine or when it darkens on standing due to oxidation of urobilinogen to urobilin.
4. Various degrees of splenomegaly.
5. Leg ulcers & gall stones are rare complications of some H.A. as S.C.A., thalassemia major & congenital spherocytosis.

B. Laboratory:
1. Evidences of increased Hb breakdown:
   - Hemoglobinemia (raised plasma Hb level especially in intravascular hemolysis).
     Hemoglobinuria & reduced plasma level of haptoglobin (a plasma protein which binds free Hb to form complexes which are rapidly cleared by RES).
   - Raised serum bilirubin (mainly indirect bilirubin). Predominantly direct hyperbilirubinemia should raise the possibility of obstruction by a gall stone.
   - Hemoglobinuria, when the amount of the released Hb exceeds the binding capacity of haptoglobin.
   - Raised urine urobilinogen.
   - Hemosiderinuria, detected as hemosiderin granules excreted in urine in chronic H. A.
2. Evidences of increased erythropoiesis:
   - Reticulocytosis, due to increased production & earlier release from bone marrow.
   - Increased normoblasts in the peripheral blood.
   - Bone marrow expansion, may produce, frontal bossing, mongoloid facies, bone pain & increased liability for fracture.
3. Morphological abnormalities of the R. C.:
   - Spherocytes are predominant in congenital spherocytosis, but may be present in other acquired H. A.
   - Elliptocytosis occurs in congenital ovalocytosis & rarely in the other forms of H. A.
   - Sickle cells in S. C. A.
   - Fragmented RC in hemolytic uremic syndrome.
   - Target cells, in thalassemia, HbC & S.C.A.
   - Siderocytes occur in some hemolytic anemia after splenectomy. (siderocytes are reticulocytes which contain iron granules, which are confirmed by “Prussian blue reaction”)
4. Evidences of shortened RC survival;
   - Using 51Cr is the most accurate confirmation of the presence of hemolysin.
5. Evidence of increased hemolysis;
   - Can sometimes be detected by osmotic fragility test, which is significantly helpful in the diagnosis of congenital spherocytosis.
Congenital Spherocytosis

- An A.D. inherited disorder characterized by R.C. stromal protein (spectrin) deficiency which makes the R.Cs. become spherical, rigid & more prone to splenic sequestration where they easily lyse.
- An abnormality in the R.C. membrane which makes it unduly permeable to sodium is also believed to be responsible. The increased intracellular concentrate of Na results in the extra utilization of ATP to extrude this Na excess from the R.C. This over work increases the vulnerability of the R.C. to destruction.

Clinical picture

- Various degrees of anemia, jaundice & splenomegaly are the 3 most important clinical features.
- In about 50% of cases hyperbilirubinemia may occur early in the neonatal period, jaundice may be so severe to necessitate exchange transfusion.
- During early infancy anemia of this condition will in addition to the physiological anemia at this age, produce severe anemia.
- Presence of mild jaundice & palpable spleen are helpful clues to the diagnosis.
- Aplastic crisis is characterized by sudden bone marrow hypoplasia which lasts 10-15 days & is commonly precipitated by infection.
- Hemolytic crisis is less common & is characterized by a rapid increase in the rate of hemolysis. This crisis is also precipitated by infections.
- Gall stone & leg ulcers are rare during childhood.

Lab. Investigations

- Peripheral film shows microcpherocytes (R.C. without central pallor).
- MCH is normal but MCHC is increased.
- Increased reticulocyte count (except during aplastic crisis).
- Increased S. indirect bilirubin.
- Increased osmotic fragility, which becomes more exaggerated after R. C. incubation for 24 hour.
- Negative coombs test, an important differentiating test from autoimmune H.A. & from ABO incompatibility in neonates in which conditions spherocytes may be seen.
- Hb electrophoresis shows normal Hb A.

Treatment

- Splenectomy is the corner stone of the treatment of congenital spherocytosis.
- Splenectomy nearly completely alleviates anemia & the accompanying symptoms. The crisis also disappears; it also prevents gall stone formation, although spherocytosis & increased osmotic fragility however persist.
- Splenectomy is better to be postponed until 5 years of age as this increases susceptibility to fulminanat infections, except when severe anemia impairs growth or aplastic crisis are frequent.
- Before splenectomy blood transfusion, as required in addition to folic acid supplement are essential.
- Splenectomized patients must receive prophylactic penicillin & polyvalent pneumococcal vaccine.
Hereditary Elliptocytosis (Ovalocytosis) (HE)

- This is a rare AD, inherited disorder affecting one in 25000 of the population, but hemolysis occurs in only 10% of them.
- The exact cause is unknown, but a protein or a lipid defect in the R.C. membrane has been claimed. 50–90% of the RC are elliptocytes (oval in shape).
- Anemia, jaundice & splenomegaly are the main manifestations in symptomatic cases.
- Reticulocyte count is increased, but the osmotic fragility test & autohemolysis are normal.
- The conditioned needs to be differentiated from; iron deficiency anemia, thalassemia, megaloblastic anemia, anemia with chronic diseases, in which mild elliptocytosis is seen.
- Prognosis is good as longevity is not affected.
- Splenectomy cures the symptomatic case like in congenital spherocytosis.

Other rare R.C. shape defect which may cause H.A. includes:

- **Hereditary stomatocytosis;** AR or AD in which RC with a slit- like central pallor predominates in the peripheral film. Some patients are symptomatic with anemia, jaundice & splenomegaly. Splenectomy may be beneficial.
- **Hereditary acanthocytosis;** an AR rare disorder in which there is marked irregularity of the RC surface. It’s seen in a syndrome called “a- betalipoproteinemina” which is characterized by:
  - Steatorrhoea (only fat malabsorption), nervous system degeneration with weakness, ataxia & nystagmus, an atypical retinitis pigmentosa with macular atrophy which results in blindness.
  - Symptoms are present since infancy & the condition is fatal during childhood.
  - S. level of cholesterol is low & there is absence of plasma betalipoprotein & triglyceride.

**Red cell enzyme defects**

The 2 most common RC enzyme deficiencies responsible for H A are G6PD & pyruvate- kinase deficiency.

1. **G6PD deficiency**

   - This is an acquired type of H A which is caused by genetic deficiency of G6PD.
   - Hemolysis in the susceptible patients occurs after the administration of one of the following:
     - Fava beans (ingestion or inhalation of its pollen), (Favism)
     - Aspirin
     - Sulphonamide as bactrim, & some food coloring agents which also contains sulfa.
     - Furadantin & furazolidone
     - Nalidixic acid (nigram)
     - Paracetamol
     - Antimalarials especially primaquine.
     - Vit.K
     - Phenacetin.
     - Chloramphenicol.
     - Naphthalene.
     - Ciprofloxacin.
   - The basic defect in this disease appears to be the production of an unstable (qualitatively different) enzyme, which becomes inactive much more rapidly than normal. That is why it is present in a reasonably active form in the young R.B.C. but not in the older ones.
   - The disease is inherited as an X- linked character with incomplete dominance & thus affects males more than females.
• It is more prevalent in negroes, Mediterranean, middle east & african children.
• H.A. follows administration of the mentioned agents by 1-3 days, associated, in severe cases, with jaundice, nausea, vomiting, epigastric pain & dark colored urine (hemoglobinuria).
• G6PD may be the cause of indirect hyperbilirubinemia & kernicterus in neonates even in absence of any trigger agent.
• Spontaneous recovery after childhood is a rule in the majority of the mild & moderate forms even if the administration of the responsible agent is continued.
• It is strange that some patients give history of fava bean consumption in the past without any evidence of hemolysis, this is probably because G6PD is an essential but not the only factor, (at least in some patients) to cause hemolysis.
• In one of the variants of G6PD, the affected patients suffer from a chronic non-spherocytic H.A in which anemia occurs even without exposure to drugs or consumption of fava bean.
• It is this type which causes neonatal jaundice & some times hemolysis occurs after febrile illnesses.

Laboratory investigations

• Rapid drop in Hb & R.C. counts
• Raised reticulocyte count
• Hemoglobinemia & hemoglobinurea
• Absent haptoglobin
• G6PD enzyme activity is diminished in the blood. This estimation should not be done before several weeks after the episode of H.A. as the newly formed young red cells are not deficient in the enzyme.

Treatment:

• Blood transfusion
• Sodium bicarbonate; to alkalinize the urine, to prevent precipitation of the acid hematin in the renal tubules & consequence renal failure.
• The known patients should avoid oxidant agents unless they are absolutely necessary.

2. Pyrovate Kinase Deficiency

• An A.R. disorder which may present in the neonatal period as jaundice & anemia.
• During infancy & childhood anemia, jaundice & splenomegaly are present.
• Osmotic fragility is normal.
• Reticulocytosis is present, with erythroid hyperplasia in the bone marrow.
• Diagnosis is confirmed by demonstration of reduced P.K. enzyme activity in the R.C.
• Treatment: The severity of the disease decreases after childhood
  o Exchange transfusion may be required in neonates.
  o Blood transfusion on need
  o Folic acid supplement
  o Splenectomy

3. Pyrimidine-5-nucleotidase enzyme deficiency.


• These last 2 forms are both very rare.
Paroxysmal Nocturna Hemoglobinurea (PNH)

- A rare chronic H.A. in which hemolysis is characteristically worse during sleep, as R.C. becomes more susceptible to hemolysis in an acid medium.
- Reduced R.C. acetyl choline esterase has been demonstrated, in addition to an abnormality in the stromal protein.
- Pancytopenia is usually present; Infection & venous thrombosis are known complications.
- Splenectomy is of no value & blood transfusion may be only helpful when required.

Paroxysmal Cold Hemoglobinurea (PCH)

- A rare form of H.A. in which acute hemolysis may occur during viral illnesses on exposure to cold.
- The disorder is due to the presence of hemolysins.
- Coombs test is +ve.
- Avoiding cold exposure is the only way to deal with this disease, as whole blood transfusion may precipitate hemolysis of both the patient and the transfused R.B.C.

March Hemoglobinurea

- A rare mild disease, in which heavy strenuous exercise in the erect posture results in H.A & hemoglobinurea, for unknown reason.
- During the episode blood examination shows; anemia, hemoglobinemia, & absent haptoglobin.
- Spontaneous recovery is the rule, but this may take several weeks.

Autoimmune Hemolytic Anemia

Unlike isoimmune H.A. which is due to mismatched transfusion & in which antibodies are infused, while in autoimmune H.A the antibodies are produced by the individual & cause hemolysis of his or her own red cells.

Etiology

1. Idiopathic.
2. Secondary e.g. leukemia, Hodgkin’s disease, NHL, lymphosarcoma, S.L.E., liver disease & some viral infections as I.M., C.M.V., mumps & mycoplasma.
3. Drug induced as penicillin, cephalosporins, antimalarials, sulphonamide & alpha-methyl-dopa.

Hemolysis is usually extra vascular & 2 major classes of antibodies are involved in this hemolysis; an IgG or worm antibody & IgM or cold antibody, these antibodies cause H.A. at 37Co & 32Co respectively.

Clinical picture

- It is rare in infants. The cardinal features in the affected children are:
- Various grades of pallor.
- Mild jaundice
- Hepatosplenomegaly
- Manifestations of the underlying disease or history of drugs in non-idiopathic forms.
- Hemoglobinurea is unusual & is suggestive of severe hemolysis.

Course & Prognosis

- Both are extremely variable ranging from a mild self-limited short lasting hemolytic anemia to a very severe & sometimes a fatal one.
- It may take a prolonged course with exacerbations.
Diagnosis

- The peripheral smear shows, spherocytosis, polychromasia& fragmented red cells.
- Decreased Hb level & R.C. count.
- Raised reticulocyte count.
- Normal to decreased platelet count.
- Bone marrow shows erythroid hyperplasia.
- Positive direct coombs test.

Treatment

1. Blood transfusion whenever required.
2. Steroid in the form of prednisolone 2-10mg/kg/day for several weeks – months.
3. Splenectomy
4. Cytotoxics when steroid & splenectomy fail. These include (Vincristine, cyclophosphamide or 6MP)

The Thalassaeimas

Thalassaemia syndrome makes a group of hereditary disorders characterized by quantitative defects in the globin chain synthesis of Hb. Its clinical manifestations result from the deceased or absent production of normal globin chains of Hb.

Beta thalassemia is caused by deceased production of beta –globin chains, while alpha thalassaemia is caused by deceased production of alpha globin chain.

Introduction:

- Normal children have 3 types of Hb; A, A2& F.
- Hb’F’ is present in the fetal blood & during the first few months of infancy.
- Hb A2 is present in extremely small quantities throughout life.
- Hb "A" is the predominant form.
- Beta thalassemia is more prevalent in the Mediterranean countries than alpha thalassemia. It results from marked reduction or complete absence of beta chain synthesis & thus Hb A. Accordingly Hb F & A2 increase in amounts to compensate for the lack of Hb. A.
- Most alpha – thalassaemia syndromes are due to deletions of the alpha-globulin genes, of which normally there are 4 (2 on each chromosome of the pair number 16).
- The severity of alpha –thalassaemias is directly proportional to the number of missing genes e.g. deletion of all results in fetal hydrops which is not compatible with life of the fetus & is associated with a great maternal morbidity.
- Thalassaemias are most prevalent in South - east Asia & Middle east countries, Greece & Italy.
- The frequency of thalassemia genes in most of these countries varies from 1 to 10 %.

Clinical picture of Beta-Thalassemia:

- Beta-Thalassemia minor is a mild form of Hypochromic Microcytic anaemia with the Hb. Level of 2-3gm. /dl. Less than the normal average for that age.
- Some ovalocytes, target cells& basophilic stippling are seen.
- Elevation of Hb.A2 levels of more than 3.5% establishes the diagnosis of Beta- Thalassemia Minor.
- No therapy is required for this form of Thalassemia.
• **Beta- Thalassemia Major (Cooley's anemia)** on the other hand is clinically characterized by progressive anemia during early infancy which makes regular blood transfusion necessary in order to sustain life.

• Progressive hepato-splenomegaly & progressive bone changes resulting in the characteristic thalassemic facies (frontal bossing, maxillary hyperplasia & prominent facial bones) will appear during the first few years, especially in the inadequately transfused patients.

• Delayed growth & puberty will be obvious in the inadequately treated patients.

• If untreated affected children with Beta thalassemia major life expectancy is usually not more than 3 years.

• Even those with repeated blood transfusions, most of them will have complications like;
  
  o Iron deposition e.g. cardiomyopathy, liver cirrhosis, diabetes mellitus or other endocrinial failure & hyper pigmentation of the skin.

  o R.C. & HLA antibody formation.

  o Infections as; Hepatitis, HIV & Malaria.

• In between the Major & Minor types there is what is called intermediate type (Thalassemia intermedia), which is characterized by a Hb. level of 6-8gm/dl. without transfusion.

**Alpha thalassemia:** This is a rare hereditary form of hemolytic anemia which occurs predominantly among Southeast Asians.

Alpha thalassemia can be seen in 4 different forms:

1. Silent carrier in which one alpha globin chain is deleted. Affected patients are asymptomatic
2. Alfa thalathemia minor in which 2 alpha globin chains are deleted & affected patients have mild anemia.
3. Hb-H disease in which 3 alpha globin chains are deleted. Affected patients have severe anemia at birth with elevated haemoglobin Bart (this type of Hb binds oxygen very strongly and do not release it to tissues). Anemia is life long and severe.
4. Hydrops fetalis in which 4 alpha globin chains are deleted. Only Hb Bart is formed since antenatal period causing severe prenatal anemia, anasarca & death.

**Laboratory findings of Beta thalassemia major**

- Hypochromic microcytic anemia,
- Target cells and pokylocytosis are seen.
- Increased serum indirect bilirubin,
- Increased serum iron.
- Hemoglobin electrophoresis is diagnostic. It shows increased hemoglobin F & decreased hemoglobin A.

**Treatment**

- **Blood transfusion:** Regular transfusion of packed red cells to maintain Hb level above 10gm/dl.
- This hyper-transfusion in addition of permitting normal activity and well beings, it prevents marrow expansion.
- Thalassemia major patients require on average one transfusion every 3 to 5 weeks.
- Prolonged blood transfusion will result in hemosiderosis with fatal consequences unless properly dealt with by iron chelating agents as Desferoxamine.
- Splenectomy is often necessary after 5 years of age because of the size of the organ or because of secondary hypersplenism, but it has no effects on the basic hematological disease.
- Pnumococcal vaccine & prophylactic penicillin is indicated in these patients.
- Bone marrow transfusion in successful cases may be curative
- Gene therapy as another curative therapy is under research.