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STUDY OF SICKLE CELL ANEMIA AND APLASTIC ANEMIA

Mr Abhijeet Rathod, Shubham Sundarrao Kharat, Pooja M Korade
Raosaheb Patil Danve College of Pharmacy Badnapur, Jalna.

ABSTRACT

Sickle-cell disease is one of the most common severe monogenic disorders in the world. Haemoglobinpolymerisation leading to erythrocyte rigidity and vaso-occlusion is central to the pathophysiology of this disease although the importance of chronic anaemia, haemolysis and vasculopathy has been established.

It is an inherited genetic condition by the production of abnormal hemoglobin which leads to the deformation of red blood cells into a rigid crescent shaped form these sickle shaped cells are less flexible and obstructing blood flow and ischemia and long term organ damage.The disease predominantly affects individuals of African , middle eastern.

It is a condition where the bone marrow fails to produce adequate amount of blood cells including red blood cells , white blood cells, platelets. This can be caused by autoimmune destruction exposure to toxic substances, viral infections. Aplastic anemia leads to pancytopenia . Aplastic anemia can affect individual of any age and characterized by a rapid onset and potentially life threatening complications without prompt treatment.

Aplastic anemia is an historic disease. The first patient was described bythe young Paul Ehrlich in 1885 its clinical features were described by Cabot and other pathologists in the early 20th century.

KEYWORDS: *Aplastic Anemia,Bone marrow failure, Pancytopenia, Hypocellular marrow, Reduced hematopoiesis, Stem cell damage.*

INTRODUCTION

The erythrocytes of person with Sickle cell Anemia manufactures an abnormal kindofhemoglobinwhen such RedBlood Cellsgives up itsoxygentointerstitial fluid theabnormal hemoglobin tend to lose its integrity in place of low oxygen tension and forms long stiff, rod like structure that bind erythrocyte into sickle shape.The sickle cell ruptures easily prolonged oxygen reduction May eventually cause extensive tissue damage .Furthermore because ofshape of sickle cells they tend to get stuck in blood vessels and can cut off blood supply to an organ altogether. Sickle cell anemia is characterized by several symptoms. In young children hand feet syndrome is present in which there is swelling and pain in wrist and feet[1].Aplastic anemia long historyhas produced confusing terminology. Anemia derives from early ability to measure red blood cells in hematocrit most patients have pancytopenia with decreased platelets and white blood cell. Aplastic means to the inability bone marrow to form blood. It is adisordercharacterizedbythefailureofthebonemarrowtoproduce sufficientamountsofblood cells. It can occur at any age and is associated with significant risks including life threatening infection and hemorrhage if not appropriate treated. It passed down from parents to childhood . Treatment may include immunosuppressive therapy, stem cell transplantation or bone marrow stimulants depending on the underlying cause and severity[2].

PATHOPHYSIOLOGY

- **Sicklecellanemia**

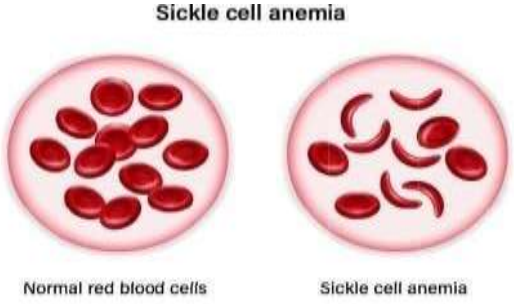

Fig.No:-1 Sicklecellanemia

Th of blood cells elasticity is central to the pathophysiology of sickle cell anemia. Normal red blood cells are quite elastic which allows the cell to deform to pass through capillaries in sickle cell anemia low oxygen tension promotes red blood cell. These cell fail to return to normal shape when normal oxygen loss tension is restored as a effect these rigidblood cells are

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unable to deform as they pass through narrow capillaries.

The actual anemia of the illness is caused by hemolysis the destruction of the red cells
Inside the spleen because of the irmisshape.Although the bonemarrowattemptstocompensate by creating new red cells it does not match the rate of destruction. Healthy red blood cells typicallylivefor 120daysbut sicklecell onlysurvive10-20 days. The keyeventsin sicklecell anemia are following Abnormal HemoglobinPolymerization.

In sickle cell anemia the substitutionof single amino acid at position six ofthe beta globin chain causes hemoglobin to form long rigid polymers when oxygen levels are low. These polymers deform red blood cells into a characteristic sickle shape which reduces their flexibility and increases their rigidity.

A) MicrovascularOcclusionandIschemia

- **Apla**

Thesickleshaped red blood cell areless deformableand cannot easilypassthrough small blood vessels leading to vascular occlusion. The obstruction of blood flow causes tissue ischemia resulting in episodes of severe pain known as vasooclusivecrises.These crises can affect various organs including lungs,bone ,spleen ,kidneys and brain.

B) Hemolysis

The sickled red blood cells are fragile and have a shortened lifespan typically less than 20 days compared to the normal red blood cells lifespan of 120 days. This leads to the hemolysis or the premature breakdown of red blood cells.

C) Inflammation and EndothelialDysfunction

The sickling process and recurrent microvascular Occlusion also trigger inflammation and endothelial dysfunction which exacerbates the disease by increasing the risk of clotting and promoting futher vascular damage.[3]

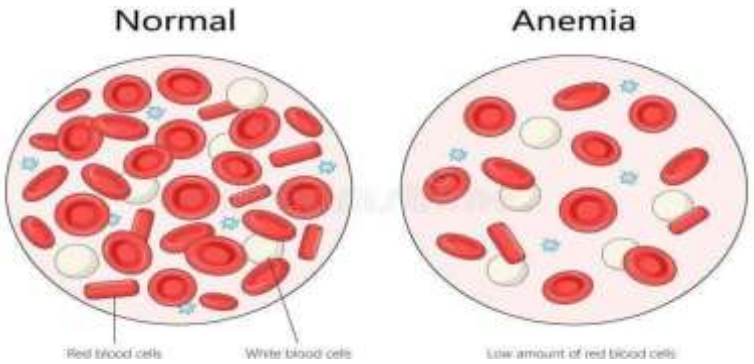

Fig. No2.Aplastic anemia

Aplasticanemiaisprimarilyadisorderofthebonemarrowcharacterizedbythefailure of the marrow to produce an adequate number of blood cells leading to pancytopenia. The pathophysiology of aplastic anemia can be categorized into immune mediated and intrinsic marrow failure mechanism.

A) BoneMarrow Hypoplasia

In aplastic anemia the bone marrow become hypocellular meaning that it has reduced number of hematopoietic stem cells and progenitor cells .This leads to an inability to produce sufficient mature blood cells. The marrow decreased cellularity may result from a direct failure in the blood cells production.

B) ImmuneMediatedMechanism

The most common form of aplastic anemia is acquired aplastic anemia where autoimmune destruction of hematopoietic stem cell is thought to occur the immune system mistakenly targets these stem cells for destruction often mediated by T lymphocytes that recognize the hematopoietic cells as foreign

C) IntrinsicstemcellDefect

Aplasticanemiacanarisefromgeneticmutationsinbonemarrowfailure syndrome such as fanconi anemia these conditions cause defect in the DNA repair mechanisms of hematopoietic stem cells leading to their premature death.

D) CytokineImbalanceandBoneMarrowSuppression

In aplastic anemia there is an imbalance in cytokine production with an increased release of pro inflammatory cytokines such as tumor necrosis. The cytokine induced suppression contributes to further damage to the bone marrow microenvironment and inhibit normal hematopoisis.[4]

RISKFACTOR

- Sicklecellanemia

Sickle cell anemia is an inherited genetic disorder caused by mutations in the hemoglobin subunit beta gene that encodes the beta globin chain of hemoglobin. The main risk factorfordevelopingsicklecellanemiaisgeneticinheritancethoughenvironmentalandclinical factors can exacerbate the disease.

1. Intestinaldisorders

Having an intestinal disorders that affects the absorption of nutrients in small intestine such as crohn disease and celiac disease surgical removal the part of small intestine where nutrients are absorbed can lead to nutrient deficiencies and Anemia.

2. Familyhistory

A family history of sickle cell disease or carriers of sickle cell trait increases the likelihood of inheriting the disease genetic counseling is advised for family with a history of Sickle cell disease to understand the inheritance patterns are risk for offspring.

3. EnvironmentalandClinicalFactors

Low oxygen condition or high altitudes can exacerbates the

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sickling of red blood cells and trigger vasooclusivecrises.Infection sickle cell are increased risk of infection particularly from streptococcus pneumoniae,Haemophilus influenzae and neisseria meningitis due to increase the risk of severe infection.Dehydration and extreme physical stress can also trigger sickling and exacerbate symptoms leading to episode of pain or other complications.[5]

- **Aplasticanemia**

A) Acquiredaplasticanemia

a. Autoimmunedisease
Themostcommoncauseofacquiredaplasticanemiaisautoimmuneresponseinwhichthe body immune system mistakenly attacks and destroy its own hematopoietic stem cells.

b. Viralinfection
Severalviruseshavebeenlinkedtothedevelopmentofaplastic anemiaincludinghepatitis, Epstein barrvirus ,parvovirus these viruses can directly affect the bone marrow.

ExposuretoToxinsandDrugs
Exposuretocertainchemicals,medicationsorradiationcandamagethebonemarrow.

B) Inheritedaplasticanemia
Fanconi anemia : This is a rare inherited bone marrow failure syndrome that significantly increases the risk of developing aplastic anemia. Fanconi anemia is typically diagnosed in childhoodandisassociatedwithdevelopment abnormalitiesandincreasesrisk of leukemia.

C) Ageandgender
Aplastic anemia can occur at anyage but children and young are more commonlyaffected by inherited forms of the disease.[6]

TYPES

- Sicklecellanemia

Sickle cell anemia are a group of inherited disorders that result from mutations in the hemoglobin subunit beta gene encoding the beta globin chain of hemoglobin. The mostcommon type of Sickle cell disease in homozygous Sickle cell disease.

a. HomozygousSicklecell anemia.
b. Hemoglobinsubunitbetaanemia
c. sicklehemoglobin-canemia
d. Sicklecell trait
e. Sicklebetathalassemia.[7]

- Aplasticanemia

Aplasticanemiaisadisorder characterizedbythefailureof the bonemarrow to produce adequate number of blood cells leading to pancytopenia**.**

A) Inheritedaplasticanemia
- Fanconianemia
- Dyskeratosiscongenita
- ShwachmanDiamondsyndromeDiamond Black fan anemia

B) Acquiredaplasticanemia
- Idiopathicanemia
- Druginducedaplasticanemia
- Infectionrelatedaplasticanemia.[8]

SYMPTOMS

- **Sicklecellanemia**

Sickle cell anemia is a genetic disorder resulting from the presence of hemoglobin theabnormal hemoglobin causesredbloodcells tobecomerigid andsickleshaped. Which leads to various complications. The symptoms of Sickle cellanemia are following.

- Swellingofhandsandfeet
- Frequentinfections
- Stroke
- Delayedgrowthandpuberty
- Jaundice
- Enlargedspleen
- Vision problems.[9]

- **Aplasticanemia**

Aplastic anemia is a condition where the bone marrow fails to produce enough blood cells leading to pancytopenia. Symptoms levels of these blood components. Thesymptoms of aplastic anemia are following.

- Fatigueandweakness
- Shortnessof breath
- Paleskin
- FrequentInfection
- Headache
- Fever
- Rapidheart rate
- Easybruisingandbleeding.[10]

DIAGNOSTICTESTS

- Sicklecellanemia

Sickle cell anemia is diagnosed through blood test and genetic testing as it is primarily a genetic disorder caused by mutations in the hemoglobin subunit beta gene encoding the beta globin chain of hemoglobin.

- Physicalexamtest
- HemoglobinElectrophoresis
- Completebloodcount
- Peripheralbloodsmear
- DNATesting
- Newbornscreening
- BonemarrowExamination .[11]

- Aplasticanemia

Aplastic anemia is a condition characterized by pancytopenia due to bone marrow failure diagnostictest focuson assessingtheseverityofbonemarrowsuppressionrulingoutother causes. Following test to identify the aplastic anemia.

- Completebloodcount
- Bonemarrowbiopsy
- Reticulocytecount
- Viraltesting
- Genetictesting
- Drugtesting
- Liverandrenalfunctiontest.[12]

CAUSES

- Sicklecellanemia

Sickle cell anemia is primarily a genetic disorder caused by mutations in the hemoglobin subunit betagene that encodes the beta globin chain of hemoglobin .The mutations leads to the production of abnormal Hemoglobin which caused red blood cell to adopt a rigid, sickle shape , leading to the clinical manifestations of the disease.

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- Geneticmutationsinthehemoglobingene
- Inheritancepatterns
- Environmentalandphysiologicaltriggers
- ComplicationsleadingtoSicklecellcrises

VasoOcclusivecrisesisaresultofthesicklecellblockingbloodflow leadingtoischemia pain and organ damage. Other complications included following.

- Acutechestsyndrome
- Splenicsequestration
- Stroke

The primary cause of Sickle cell anemia is genetic mutations, various environmental and physiological triggers can exacerbate symptoms particularly during Sickle cell crises. These are included following.

Infection

- Dehydration
- Extreme temperatures
- Hypoxia
- Stressandphysical trauma.[13]

- Aplasticanemia

Aplastic anemia is characterized by bone marrow failure that result in pancytopenia (a deficiency in red blood cell, white blood cell , platelets) . The causeof aplastic anemia can be broadly categorized as acquired and inherited though the majority of cases are acquired.below are the primary causes .

A) Acquiredaplasticanemia

a. Autoimmunemechanisms

In some cases the immune system mistakenly attacks the bone marrow leading to reduced blood cell production. This is thought to the most common cause of acquired aplastic anemia.T-cellmediatedimmunedestructionofhematopoieticstemcellsinthe bonemarrow is a key mechanism in immune Mediated aplastic Anemia. This immune response leads to bone marrow failure.

b. Viralinfections

- Certain viruses can directly infect the bone marrow or trigger immune responses that lead to bone marrow suppression. Common viruses associated with aplastic anemia include.
- Parvovirus B19 : This virus primarily affects red blood cell precursors causing a temporary halt in red blood cell production. inimmunocompromised individuals thiscan progress to more severe bone marrow suppression.
- Hepatitis viruses: Hepatitis infection can trigger an autoimmune response against the bone marrow leading to aplastic anemia
- Epstein barrvirus : Epstein barr virus has been implicated in cases of post viral aplastic anemia.

c. Drug inducedaplasticanemia:

- Certainmedicationstosuppressiontheaplasticanemiai nclude. chloramphenicol
- ChemotherapyagentAnticonvulsant
- Nonsteroidalantiinflammatorydrug
- Thesedrugcancausedirecttoxicitytothebonemarrowo rleadtoanimmunemediated reaction against hematopoietic stem cells.

B) Inheritedaplasticanemia

Inherited forms of aplastic anemia are relatively rare but are important to diagnose due to the specific management strategies required.Themostwell-known in herited formsinclude.

a. Fanconi Anemia:

Thisisaninheriteddisordercausedbymutationsingenesresponsibl eforDNArepairleadingtodefectiveDNArepairmechanismsandin creasedriskofbonemarrowfailure Individuals with Fanconi anemia often have skeletal anomalies short stature and increased susceptibility to cancers(e.g. leukemia).

b. Shwachman-DiamondSyndrom:

A genetic disorder that causes exocrine pancreatic insufficiency and bone marrow failure. Individuals with this syndrome can develop pancytopenia and are at increased risk of leukemia.

c. DyskeratosisCongenita:

Thisisanotherinheriteddisordercharacterizedbydefectivetelome remaintenanceleadingto premature cell aging and bone marrow failure. It is associated with skin pigmentation abnormalities nail dystrophy and oral leukoplakia.

d. Diamond-BlackfanAnemia:

Thisisarareinheriteddisorderthataffectstheproductionofredbloo dcellsduetodefectiveerythropoiesis.Itresultsinsevereanemiaand affectedindividualsmayrequirelifelongblood transfusion.[14]

TREATMENT

- SickleCellAnemia

The treatment of Sickle Cell Anemia focuses on managing symptoms preventing complications and improving the quality of life. The management approach includes pharmacologic therapies, blood transfusions, bone marrow transplant, and supportive care. The goal is to reduce the frequency of painful episodes minimize organ damage and provide supportive care during acute events.

a. HydroxyureaTherapy

Hydroxyureaisthe most widelyused drugforthe managementofsickle celldisease. It works by increasing the production of fetal hemoglobin which inhibits the sickling of red blood cells. Increased hemoglobin levels reduce the occurrence of sickling and vaso-occlusion.

b. BloodTransfusions

Regular blood transfusions are used in patients with severe disease to reduce the proportion of sickle cells and prevent complications such as stroke and acute chest syndrome.

c. BoneMarrow orStemCellTransplantation

Hematopoieticstemcell transplantation(HSCT)istheonlypotentialcurativetreatmentforsi ckle cell anemia. It involves replacing the patients bone marrow with that from a matched sibling or an unrelated donor.

d. PainManagement

Pain crisesarea hallmark of sickle cell disease and can be severe. Pain management includes the use of opioids, NSAIDs, and intravenous fluids to prevent dehydration and improve circulation.Non-pharmacologic therapies such as heat therapy, physical therapy and distraction techniques can also help in pain management.

e. PreventiveMeasures

Prophylactic antibiotics eg.penicilne are recommended for children with sickle cell disease to prevent infections particularly with Streptococcus pneumoniae.[15]

f. GeneTherapy

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- **Aplasticanemia**

The treatment of Aplastic Anemia depends on whether the condition is acquired or inherited. The main goals are to stimulate bone marrow production, prevent infections and bleeding and provide supportive care. In severe cases bone marrow transplantation offers a curative option.

I. Immunosuppressive Therapy
- Acquired aplastic anemia which accounts for the majority of cases immunosuppressive therapy is the cornerstone of treatment.
- Immunosuppressive therapy has a response rate of 60-70% in young non-severe patients but the response can take several months to be evident.

II. HematopoieticStemCellTransplantation
- Patients with severe aplastic anemia bone marrow or stem cell transplantation offers the potential for a curative treatment. This is typically performed in patients under the age of 40 who have a matched sibling donor.
- Transplantation has a high success rate if performed early in the disease course particularly in younger patients.

III. SupportiveCare
- BloodTransfusions.
- Infection
- PreventionandTreatment
- GrowthFactors

IV. AndrogensandOtherStimulatingAgents

In some cases particularly in patients who cannot receive a transplant or immunosuppressivetherapy androgens (e.g. oxymetholone) or thalidomide may be used to stimulate erythropoiesis and promote bone marrow recovery.

V. ManagementofUnderlyingConditions

If aplastic anemia is secondary to an underlying condition such as hepatitis or drug exposure treating the underlying cause is crucial. This may involve discontinuing the offending drug treating the infection or managing other contributing factors.[16]

NEED OF WORK

1. GeneticDisorder:Causedbyamutationin theHBBgenethataffects hemoglobin (HbS).
2. Abnormal Red Blood Cells:RBCsbecome sickle-shaped,rigid,and sticky.
3. AutosomalRecessiveInheritance:Inheritedfrom bothparents (communing Africanand Mediterranean populations).
4. LeadstoVaso-occlusion:Sickledcellsblockbloodflow,causingpaincrisesandorgan damage.
5. HemolyticAnemia:IncreaseddestructionofRBCsleadsto chronic anemia.
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AIM: STUDY OF SICKLE CELL ANEMIA AND APLASTIC ANIMIA

OBJECTIVE

1. To understand the genetic basis and molecular mechanism of Hb Smutation.
2. To identify the clinical manifestations and complications related to sickling of red blood cells.
3. Toevaluatethecurrentmanagementapproachesincludinghydroxyurea,bloodtransfusion,andbonemarrow transplantation.
4. Toexploreemergingtherapiessuchasgeneeditingandfetalhemoglobininduction.
5. To compare and contrastSickle CellAnemia and A plastic Anemia in terms of etiology, pathophysiology, clinical presentation, and treatment outcomes.
6. Doyouwantmetoalsomakeaflowchartofobjectives(likeavisualdiagramforyourproject)soit looks more presentable?
7. GeneticDisorder:CausedbyamutationintheHBBgenethataffects hemoglobin (HbS).
8. AbnormalRed BloodCells:RBCsbecomesickle-shaped,rigid,andsticky.
9. AutosomalRecessiveInheritance:Inheritedfrom bothparents(commoninAfricanandMediterranean populations).
10. LeadstoVasoocclusion:Sickledcellsblockbloodflow,causingpaincrisesandorgandamage.

HemolyticAnemia:IncreaseddestructionofRBCsleads

RESULTS

Interviewswerecompletedon59 ofthe70 caseswho metthe diagnostic criteria. Inability to obtain a matched control using random digit dialing was the primary reason for excluding eligible cases, e.g. three who resided outside the United States and one 81-yr old white male.Thirty two(54%)caseswereinterviewddirectly;the remainder(27 or46%)were surrogates, primarily because the cases were minors (15 subjects) or were deceased (10 subjects). Forty-one (69%) controls were questioned directly; the remainder (18 or 31%) were surrogates, 16 of whom wereparentsor guardians of minors.The majority of case interviews(39or66%)were carriedoutinperson(mostlyinhospitals),whilethemajorityofcontrolinterviews(51or86%)wereconductedbytelephone, principally because most controls resided outside the Baltimore metropolitan area. The majority of the cases (73 %) were identified at The Johns Hopkins Hospital, possibly related to the presence of its Bone Marrow Transplant Unit; the remainder were found at 10 other Baltimore area hospitals. No cases were found at 14 participating hospitals despite careful search of discharge listings.

CONCLUSION

Sickle cell anemia is a hereditary condition caused by a mutation in the hemoglobin subunit beta genewhich results in the formation of hemoglobin S. This causes red blood cells tobecome rigid and sickle-shaped leading to a range of complications includingpain crises, stroke and organ damage.

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Treatments such as hydroxyurea, blood transfusions and bone marrow transplantation are central to managing the disease. While there is no universally available cure the development of gene therapy offers hope for the future. However challenges remain in expanding access to curative treatments particularly for patients in low-resource settings.Aplastic anemia on the other hand involves the destruction of bone marrow hematopoietic stem cells leading to a failure in blood cell production. The causes of aplastic anemia are varied and include autoimmune mechanisms viral infections and drug toxicity aswell as inherited syndromes. For acquired aplastic anemia immunosuppressive therapy and hematopoietic stem cell transplantation are the primary treatment modalities with hematopoietic stem cell transplantation offering a curative option for many patients. The success of hematopoietic stem cell transplantation depends on the availability of a matched donor and complications such as graft-versus-host disease remain a concern. Supportive care including blood transfusions.

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