NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

Background

1. Definition
   - Neonatal Thrombocytopenia: Platelet count <150 X 10⁹/L
   - Severe Neonatal Thrombocytopenia: Platelet count <50 X 10⁹/L

2. General Information
   - Fetal/neonatal alloimmune thrombocytopenia (FNAIT) – most common and important cause of severe neonatal thrombocytopenia

Pathophysiology

1. Pathology of Disease
   - Maternal antiplatelet IgG antibodies cross placenta and attack fetal platelets at 14-16 weeks gestation
   - Human platelet antigens (HPA) must be absent in mother and present in fetus (due to inheritance from father)
   - By 18 weeks gestation, platelet antigens seen in fetus
   - Transfer of antibodies increases as gestation progresses until maximum level is reached in late 3rd trimester
   - Severity depends on:
     - Concentration and subclass of maternal IgG allo-antibodies
     - Antigen density on fetal platelets
     - Phagocyte activity in fetal reticuloendothelial system.
     - Ability of fetal bone marrow to compensate for accelerated platelet destruction

2. Incidence, Prevalence
   - HPA-1a found in 98% of Caucasian population
   - 2% of Caucasian pregnant women are HPA-1a negative and likely to carry a HPA-1a positive fetus
   - In Asians, HPA-4 most common cause of FNAIT
   - FNAIT Incidence: 1/600-1/5000
   - Anti-HPA-1a sensitization occurs only if mother’s Human Leukocyte Antibody (HLA) type is DR52a.

3. Risk Factors
   - HPA incompatibility between father and mother

4. Morbidity / Mortality
   - Antenatal intracranial hemorrhage (ICH) in 10-30% of severe FNAIT
   - Death in 10% of ICH
   - Neurological sequelae in 10%-20% of ICH
   - 1/3 of infants with FNAIT and ICH die
Diagnostics

1. History
   - Previous pregnancy of FNAIT

2. Physical Examination
   - Healthy appearing newborn born to healthy mother with normal maternal platelet count and uneventful pregnancy
   - Within minutes to hours of newborn’s life: petechiae, bruising, excessive bleeding, and mucocutaneous purpura appear
   - ICH presentation: can vary from asymptomatic to seizures, retinal hemorrhage, lethargy, tense fontanel, altered consciousness, apnea, and bradycardia

3. Diagnostic Testing
   - Diagnosis made after birth for first pregnancy
   - CBC usually normal except for thrombocytopenia and anemia if excessive blood loss (always confirm true thrombocytopenia with second sample)
   - Platelet count <20,000/ml when symptoms appear
   - Must rule out infection, disseminated intravascular coagulation, bleeding disorders and maternal immune thrombocytopenia (ITP)
   - Confirmatory test: presence of antiplatelet antibodies in maternal blood sample + maternal-paternal antigen incompatibility
     - Mother and father should be screened for HPA-1, HPA-3, HPA-5 [+ HPA-4 if Asian]
     - Maternal antiplatelet antibody testing accomplished via:
       - Monoclonal antibody-specific immobilization of platelet antigen test (MAIPA)
       - Platelet immunoflourescence test (PIFT)
       - Antigen-specific particle assay (ASPA)
     - Serologic testing for FNAIT recommended in following scenarios:
       - severe thrombocytopenia (even when other causes of neonatal thrombocytopenia present)
       - ICH with significant thrombocytopenia
       - Family history of any transient neonatal thrombocytopenia
   - Diagnostic Testing in multiparous women with confirmed previous FNAIT
     - PCR from amniocytes or chorionic villi at 18 weeks gestation to determine fetal platelet type
     - Fetal Blood Sampling to determine severity
       - Use diminished because of significant risks
       - 1.3% fetal loss rate per procedure
       - 5.5% loss rate per affected pregnancy

4. Laboratory evaluation
   - Commercial enzyme-linked immunosorbent antibody kits for initial screen followed by monoclonal antibody specific immobilization of platelet antigen assays and radioimmunoprecipitation assay for further antibody testing

5. Diagnostic imaging
   - All neonates with confirmed FNAIT should be screened for ICH via cerebral ultrasound, CT, or nuclear magnetic resonance scan
Differential Diagnosis

1. Key Differential Diagnoses
   - FNAIT seen in healthy newborns versus thrombocytopenia seen in a sick newborn. Newborn thrombocytopenia seen in the following:
     - Maternal Idiopathic Thrombocytopenia purpura (2nd most common cause of neonatal thrombocytopenia)
     - Neonatal Drug Exposure: Heparin, Quinine
     - Thrombocytopenia – absent radius syndrome
     - Congenital Amegakaryocytic Thrombocytopenia
     - Maternal Factors:
       - Penicillin, Dioxin, Phenytoin, Indomethacin, Phenytoin, Heparin exposure;
       - History Pregnancy Induced-Hypertension
       - Chromosomal abnormalities: Trisomy 18, 13, 21, Turner’s
       - Wisckott-Aldrich Syndrome
       - Fanconi’s anemia
       - Kasabach-Merritt syndrome
       - Cardiac anomalies
       - Placental insufficiency

2. Extensive Differential Diagnoses
   - Congenital infections: CMV, Syphilis, Toxoplasmosis, Rubella, HIV, Parvovirus B19
   - Severe Rhesus disease
   - Disseminated intravascular coagulation
   - Perinatal infection: GBS, E.coli, Listeria

Therapeutics

1. Acute Treatment in Neonate
   - Treat based on newborn’s condition
     - Asymptomatic with mild to moderate thrombocytopenia
       - No treatment necessary
     - Neonatal Bleeding or Severe Thrombocytopenia
       - First Line Therapy: Transfusion of HPA compatible platelets ASAP
         - Transfusion of 1 dose (10 mL/kg) usually increases platelet count by $100 \times 10^9$ / L within 1 hour
       - If HPA compatible platelets not available, then either
         - Transfusion of HPA-1a-negative and HPA-5a-negative platelets or
         - Transfusion of maternal platelets
           - Need gamma-irradiated and washed to minimize transfer of maternal antibodies.
       - Until matched platelets available, acceptable to give unmatched platelet concentrates
       - IVIG and/or steroids when severe thrombocytopenia and/or hemorrhage persists
Therapeutic effect of platelet count delayed for 24-48 hrs; neonate remains at risk for ICH
- Fresh Frozen Plasma
  - Contains 1 international unit of clotting factors for every 10-15 mL/kg
  - Dose: 10-20 mL/kg to prevent bleeding with severe thrombocytopenia of unknown origin

2. Antenatal Treatment in history of FNAIT sibling
   - Recommend non-invasive management over invasive
     - Non-Invasive Management
       - Weekly maternal gamma globulin infusion - IVIG (1 g/kg/wk) with or without steroids (0.5 mg/kg/d)
         - Gamma globulin has following actions:
           - suppresses platelet antibody synthesis
           - blocks antiplatelet antibody transfer
           - competitively inhibits platelet binding to maternal antibodies and/or interferes with phagocyte-mediated immune clearance by reticulo-endothelial system
         - Peak maternal IgG level decreases by 50% after 72 hrs
         - IVIG prevents ICH and increases platelets in 55%-85% of cases
         - Side effects: Aseptic meningitis, acute renal failure, thrombosis, anaphylaxis, headaches, febrile reactions, nausea, malaise, and myalgia
           - Side effects minimized by slowing infusion rate
         - Optimal management with IVIG alone or IVIG plus steroids remains unclear.
     - Steroids as sole treatment controversial
       - Efficacy variable, and chronic steroid therapy associated with oligohydraminos
       - Mechanism of action: suppression of Fc receptor function of macrophages and possible interference with antibody synthesis
         - Invasive Management
           - Fetal blood sampling and intrauterine platelet transfusion
             - Previous initial approach but no longer commonly used because of the increased risk of fetal death
             - Only used as an option when mother does not respond to noninvasive management
       - Mode of Delivery
         - Delivery plan based on patient’s risk category, response to treatment, and most recent fetal platelet count.
         - Cordocentesis, to determine fetal platelet count as delivery considered, not associated with fetal bleeding
         - Appropriate gestation age for delivery has not been determined
• Cesarean Delivery alone not effective in preventing antenatal or perinatal hemorrhage
• Vaginal Delivery
  • Reasonable if fetal platelet > 50 X 10^9/L
  • If platelets <50 X 10^9/L, platelet intrauterine transfusion can protect against bleeding (must weigh risks of transfusion)
  • No evidence to suggest increased risk of ICH in vaginal deliveries with platelets <50 X10^9/L
  • Avoid instrumental vaginal delivery, fetal scalp electrodes, and fetal scalp blood samples
  • Neonatal care team should be present and compatible platelets prepared by blood bank

3. Further Management (24 hrs)
  o Observe and follow platelet counts daily^5
  o Maternal antibodies start to leave infant’s circulation at 48 hours of age^3
  o Resolution of FNAIT usually occurs by 2 weeks of age with complete normalizing of platelet count by 4 weeks^3
  o Platelet count should be kept > 100 X 10^9/L if bleeding occurred and maintained at >50 X 10^9/L for 1 to 2 weeks^5

4. Recommended Antenatal Therapy.\(^1\)
  o Weekly maternal IVIG infusions (1 g/kg/wk) with or without oral steroids (0.5 mg/kg/d)
  o Begin treatment 4 to 6 weeks earlier than when ICH or severe thrombocytopenia occurred in previous pregnancy
    • If information unavailable begin therapy at 30 weeks

Follow-Up^3
1. Outpatient follow-up includes platelet levels for rare but possible thrombocytopenia recurrence
2. Developmental/neurological follow-up is necessary if ICH occurred
3. Close maternal follow-up with high risk obstetrics and early prenatal care if history of confirmed FNAIT pregnancy

Prognosis
1. FNAIT occurs earlier and is more severe in subsequent pregnancies^1
2. Recent studies show that high 3rd semester antibody titers (>1:32) and high IgG3 subclass titers may predict severe thrombocytopenia. This has yet to be confirmed.\(^6\)
3. Best noninvasive predictor = in utero ICH in sibling\(^1\)
   o 70-80% recurrence rate of ICH if prior sibling affected\(^1\)
4. Quick and proper treatment reduces the risks of death and long-term disabilities^3

Patient Education\(^1\)
1. Must provide preconceptional counseling for patients with history of pregnancy with FNAIT
References

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