NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

Background

1. Definition[1]
    - Neonatal Thrombocytopenia: Platelet count <150 X 10^9/L
    - Severe Neonatal Thrombocytopenia: Platelet count <50 X 10^9/L
2. General Information
    - Fetal/neonatal alloimmune thrombocytopenia (FNAIT) – most common and important cause of severe neonatal thrombocytopenia[2]

Pathophysiology

1. Pathology of Disease
    - Maternal antiplatelet IgG antibodies cross placenta and attack fetal platelets at 14-16 weeks gestation[3]
    - Human platelet antigens (HPA) must be absent in mother and present in fetus (due to inheritance from father)[3]
    - By 18 weeks gestation, platelet antigens seen in fetus[3]
    - Transfer of antibodies increases as gestation progresses until maximum level is reached in late 3rd trimester[1]
    - Severity depends on[1]:
        - 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[1]
    - 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[3]
4. Morbidity / Mortality[1]
    - 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[3]

Diagnostics

1. History[1]
    - Previous pregnancy of FNAIT
2. Physical Examination
    - Healthy appearing newborn born to healthy mother with normal maternal platelet count and uneventful pregnancy[1]
    - Within minutes to hours of newborn's life: petechiae, bruising, excessive bleeding, and mucocutaneous purpura appear [3]
    - ICH presentation: can vary from asymptomatic to seizures, retinal hemorrhage, lethargy, tense fontanel, altered consciousness, apnea, and bradycardia[3]
3. Diagnostic Testing
    - Diagnosis made after birth for first pregnancy[3]
    - CBC usually normal except for thrombocytopenia and anemia if excessive blood loss (always confirm true thrombocytopenia with second sample)[3]
    - Platelet count <20,000/ml when symptoms appear[3]
    - Must rule out infection, disseminated intravascular coagulation, bleeding disorders and maternal immune thrombocytopenia (ITP)[1]
    - Confirmatory test: presence of antiplatelet antibodies in maternal blood sample + maternal-paternal antigen incompatibility[1]
        - Mother and father should be screened for HPA-1, HPA-3, HPA-5 [+ HPA-4 if Asian][3]
        - Maternal antiplatelet antibody testing accomplished via:
            - Monoclonal antibody-specific immobilization of platelet antigen test (MAIPA)
            - Platelet immunofloursecence test (PIFT)
            - Antigen-specific particle assay (ASPA)
        - Serologic testing for FNAIT recommended in following scenarios:[1]
            - 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[1]
        - Fetal Blood Sampling to determine severity[4]
            - Use diminished because of significant risks
            - 1.3% fetal loss rate per procedure[4]
            - 5.5% loss rate per affected pregnancy[4]
4. Laboratory evaluation[5]
    - 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[3]
    - 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[3]
    - 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[1]
    - 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 [1]
        - Asymptomatic with mild to moderate thrombocytopenia[1]
            - No treatment necessary
        - Neonatal Bleeding or Severe Thrombocytopenia
            - First Line Therapy: Transfusion of HPA compatible platelets ASAP[1]
                - Transfusion of 1 dose (10 mL/kg) usually increases platelet count by 100 X 10^9/ L within 1 hour
            - If HPA compatible platelets not available, then either [1]
                - 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[1]
            - IVIG and/or steroids when severe thrombocytopenia and/or hemorrhage persists[1]

        - Therapeutic effect of platelet count delayed for 24-48 hrs; neonate remains at risk for ICH
    - Fresh Frozen Plasma[3]
        - 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[1]
        - Non-Invasive Management
            - Weekly maternal gamma globulin infusion - IVIG (1 g/kg/wk) with or without steroids (0.5 mg/kg/d)[1]
                - 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[1]
                - Peak maternal IgG level decreases by 50% after 72 hrs[1]
                - IVIG prevents ICH and increases platelets in 55%-85% of cases[1]
                - Side effects: Aseptic meningitis, acute renal failure, thrombosis, anaphylaxis, headaches, febrile reactions, nausea, malaise, and myalgia[1]
                - Side effects minimized by slowing infusion rate[1]
                - Optimal management with IVIG alone or IVIG plus steroids remains unclear.[2]
            - Steroids as sole treatmentcontroversial[1]
                - 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[2]
            - 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[1]
        - 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[1]
            - 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)
    - Observe and follow platelet counts daily[5]
    - Maternal antibodies start to leave infant's circulation at 48 hours of age[3]
    - Resolution of FNAIT usually occurs by 2 weeks of age with complete normalizing of platelet count by 4 weeks[3]
    - 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]
    - Weekly maternal IVIG infusions (1 g/kg/wk) with or without oral steroids (0.5 mg/kg/d)
    - 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]
    - 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
2. http://naitbabies.org/

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Author: Sneha Kemkar, MSIII, & James Hynes, MD, *University of TN COM*

Editor: Robert Marshall, MD, MPH, MISM, CMIO, *Madigan Army Medical Center, Tacoma, WA*