Dx: Afibrinogenemia

A Rare Encounter

Mary Ryan, MT (ASCP), CLS II
Saint Luke’s Northland Hospital
Saint Luke’s Northland Hospital
Part of the Saint Luke’s Healthcare System
Kansas City, Missouri

- 95 bed hospital
- 20 specialized healthcare services
- 9 Private Birthing Rooms
- Level II Neonatal Intensive Care Unit
Laboratory Services

• Staffed 24/7
• 2-4 Clinical Laboratory Scientists per shift
• Generalists with 1 SH
• Routinely Stock
  – FFP
  – RBC’s;
  – Pooled Cryo-A and O;
  – Plts for Cath Lab procedures
It was a dark and stormy night...

- OB Nursing Supervisor called
- C-section of infant with possible Dx of afibrinogenemia
- 48 hours to prepare
- Received history of family
- 24 y/o female G4 P0 Ab1 LC2 mother
Mother’s History with #1 Baby Girl

• Blood type A POS
• Adequate prenatal care-started at 9 weeks gestation
• Complications included:
  – Pre-eclampsia
  – Chronic Abruptio,
  – Hypertension
  – Proteinuria
• Induced delivery at 35 weeks at another large trauma center in KC
#1 Baby Girl

- Pre-term vaginal delivery,
- Vacuum Extraction x 3 and placental abruption
- Weight 2.065 kg or 4.552 lbs
- Apgar Score: 6 at 1 minute and 8 at 5 minutes
- Cord pH was 7.21; Cord pC02 was 48
- At delivery newborn was cyanotic and grunting
- Treatment at delivery included stimulation and oxygen
- Admitted to NICU
#1 Baby Girl Complications Arise

- Bleeding from PIV and vascular stick sites that did not stop with pressure dressings
  - Hgb 13.5        PT > 17;        Plt 134
  - HCT 41.8       PTT >25

- Neonatal consult
- Repeat labs: Hgb 12.9; Hct 38; Plts 168
- FFP transfused 20 ml (10 ml/kg)
- Patient transported to Children’s Mercy Hospital in KCMO
#1 Baby Girl at CMH

- Hgb 6.6, Hct 19.5, Plts 95
- Hematology/Oncology consult
- Transfused
  - pRBC 15 ml/kg;
  - platelets 10 ml/kg;
  - Vitamin K given
- CT showed subdural and subarachnoid hemorrhage
Coag Results for # 1 Baby Girl

- Fibrinogen activity---low at 72
- Fibrinogen antigen---low at 83
- FDP-normal
- Fibrinogen inhibitors-normal
- Factors 2, 5, 7, 8 and 10 with mixing studies ordered--all factors normal
- Plasminogen activator-inhibitor-normal
- Euglobin in clot lysis-normal
- 2-antiplasmin activity-normal
Mother and Father Tested

<table>
<thead>
<tr>
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<th>Mother</th>
<th>Father</th>
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<tbody>
<tr>
<td>Fibrinogen activity</td>
<td>Normal 183</td>
<td>Borderline 159 (Ref 164-382)</td>
</tr>
<tr>
<td>Fibrinogen antigen</td>
<td>Normal 206</td>
<td>Slightly low 167 (Ref 180-400)</td>
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Based on this information, doctors thought dysfibrinogenemia or hypofibrinogenemia unlikely.
## Congenital Abnormalities of Fibrinogen

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
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<tbody>
<tr>
<td>Hypofibrinogenemia &amp; Afibrinogenemia</td>
<td>Dysfibrinogenemia &amp; Hypodysfibrinogenemia</td>
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<tr>
<td>– <em>Quantitative abnormality</em></td>
<td>– <em>Qualitative abnormality</em></td>
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<tr>
<td>– Affects fibrinogen</td>
<td>– <em>Dysfunctional fibrinogen</em></td>
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<tr>
<td>concentration</td>
<td>– <em>Results in bleeding or thrombosis</em></td>
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<tr>
<td>– Associated with bleeding</td>
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<td>diathesis</td>
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Inherited Abnormalities of Fibrinogen

- Congenital afibrinogenemia is the result of defective fibrinogen synthesis
- Total absence of measurable fibrinogen in plasma
- Autosomal-recessive trait
- Initial symptoms include bleeding from umbilical cord stump
- Other symptoms include intracranial bleeding, epistaxis, and GI bleeding.
Fibrinogen Function

- Primary role is hemostasis
- Limits bleeding at sites of blood vessel injury
- Provides structure for assembly and activation of the fibrinolytic proteins
- Non-substrate thrombin binding sites—after clot formation promotes the antithrombotic properties of fibrinogen
- Platelet aggregation
- Fibrinolysis
#1 Baby Girl at CMH

- **Dx:** Severe Periventricular Encephalomalacia
  - *a softness or degeneration of brain tissue, as caused by impairment of the blood supply.*

- **Cryoprecipitate**—every other day while hospitalized

- Hospitalized almost 2 months

- Cryo transfusions every other week as outpatient

- Discharge Med: Phenobarbitol

- Outpatient consults with Ophthalmology, Pediatric Hematology, Pediatric Neurology and Pediatrician
Parents Eventual DX

Mother
- Mild Hypofibrinogenemia
- 5 months post partum
  Fibrinogen Antigen level
  185 (ref 180-400)
- 5 month Fibrinogen
  Activity level not
  available

Father
- Mildly low fibrinogen
  levels
- CBC
  - Plt 174 (150-400)
  - Diff: Sickle; Sphero;
    Oval; Target; Burr;
    Teardrop; Stippling; HJ
    Bodies; Hypersegs;
    Toxic Gran; Vac Neut;
    Dohle; Giant Platelets
Inherited Hypofibrinogenemia

- Patients are usually asymptomatic
- May have a history of bruising easily, nosebleeds
- Menorrhagia
- Possible spontaneous abortions
- Patient’s reference point for normal is family
Plasma Sources of Fibrinogen

Fibrinogen concentrates and cryoprecipitate are both derived from human plasma.
- Concentrates offer the advantage of virus inactivation.
- More precise dosing achieved with Concentrates.
- Individualized therapy needed with either product.
Cryoprecipitate

• Human plasma product—not virus inactivated
• Contains Factor VIII, Factor XIII, Fibrinogen, von Willebrand factor, and Fibronectin
• Each bag provides 100-250 mg fibrinogen
RiaSTAP CSL Behring

• Approved by FDA in 2009
• Treat acute bleeding episodes in patients with congenital fibrinogen deficiency
• Not indicated for dysfibrinogenemia
• Single use vials contain 900-1300 mg lyophilized fibrinogen concentrate powder for reconstitution
#1 Girl at 4 years old

- Dx: Homozygous Inheritance of Hypofibrinogenemia-leading to Afibrinogenemia
- Developmental Delay
- Had received RiaSTAP—developed bad reaction---2 hours of unresponsiveness
- Seizure free for past year
- Developed allergy to phenobarbital-on Keppra
- Amicar (Aminocaproic Acid) for mouth injuries and dental procedures
#2 Baby Boy

- At birth fibrinogen level of 127 mg/dl - low
- No significant bleeding problems
- Circumcised with no bleeding problems

Dx: Hypofibrinogenemia—Heterozygotic

- Does not expect spontaneous bleeding except after surgery or trauma
- No need for scheduled cryoprecipitate infusions
- Described as active, alert, with no distress
Baby #3—48 hours before delivery

- Case history received
- Instructions from Region VII Hemophilia Program
- Request Fibrinogen at birth—without risk of VP to infant via Cord blood
- Neonatologist from CMH to be in attendance
- Recommended delivery method
  - No vacuum, minimize trauma
  - Cesarean Section
- Only CBC & Type and Screen performed on Mother the day before delivery; No Coag testing
Cord Blood Collection Procedure

1. Double clamp umbilical cord in 2 places-one near infant & other near placenta
2. Draw blood from cord using Vacutainer
3. Draw 1 red gel & discard.
4. Use 2.7 ml NaCitrate for 2nd draw-draw 2
5. Send to lab STAT
CLAMPING PROCEDURE FOR THE COLLECTION OF CORD BLOOD

After double-clamping the cord, cut between the clamps and remove the segment (see diagram below). Draw 1-2 ml. of blood from the umbilical vein and discard. With the needle still in place, draw 4.5 ml. of blood into a properly citrated syringe or blue top vacutainer (be sure to discard the first blood). Then proceed with steps 4-8 on page one.

Segment of the cord should be as long as possible or about 10 inches.

Clamp

Clamp

Clamp

Clamp

Placenta

Newborn child

Cut between clamps.
St. Lukes Northland Lab’s Role

• Consult with our Pathologist
• Blood type of newborn unknown
• Obtain 3 units AB Cryoprecipitate
• Be prepared to run Fibrinogen Stat
• Dispense Cryo if needed
Availability of AB Cryo

• CBC initially said none was available
  – Gave patient HX and reason for request
  – Said they would call me back

• ARC said they would call me back

• CBC called back first--was able to obtain the 3 units from CMH stock
#3 Baby Girl  Delivered

- Uneventful C-section
- No reported bruising or bleeding on baby but oozing started on cord blood stick site
- Labs (performed on cord blood):  STA Stago
  - Protime >150 (11.7-14.3); C
  - INR > 22 (0.9 – 1.1); C
  - APTT > 200 sec (22-34)  C
  - Fibrinogen <100 mg/dl C
- Cryo—1 unit issued
- CBC on Capillary draw: Hgb 15.5 g/dl; Hct 44%; Plt 198 (140-400 TH/ul)
#3 Baby Girl at CMH

- Newborn transferred to Children’s Mercy
- Fibrinogen 80
- Baby last reported with unstable labs
- Baby #3 currently being treated along with her sister at the Hemophilia Clinic
What are the odds?

- Afibrinogenemia accounts for 24% of inherited Factor I deficiencies
- Hypofibrinogenemia and Dysfibrinogenemia were each 38%
- Afibrinogenemia is estimated to be 1 in a million live births
Resources

- Region VII Hemophilia Program—KC Regional Hemophilia Center
  816-234-3508

- National Hemophilia Foundation
  800-42-HANDI (www.hemophilia.org)

- Midwest Hemophilia Association
  800-431-7960
  (www.midwesthemophilia.org)