Post-operative bleeding in a patient with factor XIII deficiency and Noonan syndrome: a case study

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Introduction: What is Factor XIII deficiency?

• Factor XIII
  • Also known as *fibrin stabilizing factor* (strengthens the final stages of hemostasis).
  • Plays a pivotal role in angiogenesis, maintenance of pregnancy, wound healing, bone metabolism and cardio protection.

• Congenital or acquired deficiency
  • Autosomal recessive or inhibitor/antibody

• Major Symptom
  • Hemorrhagic diathesis

• Incidence
  • 1:1,000,000 to 1:5,000,000 (consanguineous marriage ↑ incidence)

• Treatment options
  • Factor XIII concentrate, rFXIII, FFP, blood transfusion
Important note: bleeding time, aPTT, PT and other preliminary coagulation tests can be within the normal range for FXIII deficiency.
Noonan syndrome

• Inheritance
  • Autosomal dominant

• Prevalence
  • 1:1000 to 1:2500

• Affected gene
  • Most commonly due to mutations in the PTPN11 gene

• Features
  • Webbed neck, short stature, characteristic facies, congenital heart defects, and developmental delay

• Relevance
  • Proclivity for bleeding diathesis is included in the phenotypic spectrum, with platelet abnormalities and factor XI deficiency being cited most commonly
Noonan syndrome

Mutations that cause Noonan syndrome alter genes encoding proteins with roles in the *RAS–MAPK pathway*, leading to pathway dysregulation.
Characteristic Facies

Noonan’s Syndrome: Facies

- High anterior hairline
- Triangle-shaped head
- Transparent, wrinkled skin
- Prominent nasolabial folds
Case Presentation
Case presentation

• 13 year old boy w/ known Noonan syndrome
• Relevant history
  • Hepatosplenomegaly
  • Chronic thrombocytopenia
  • Hx of easy bruising
• ENT-related problems
  • Dysfunction of eustachian tube
  • Chronic serous otitis media
  • Chronic otorrhea (drainage)
  • Chronic suppurative (purulent) otitis media (CSOM)
  • Central perforation of TM on right
  • Middle ear conductive hearing loss (CHL)
• Previous ENT procedures
  • Cohen tubes x3 (ear ventilation tubes) to allow for fluid drainage and equalization of pressure
Case presentation

• Combination of recurrent ear infections and retained ear tubes led to CHL and CSOM

• Recommended treatment
  • Remove tubes and patch drums - left tympanoplasty with mastoidectomy and right myringoplasty with epidisc.
Case presentation

• Given the history of easy bruising, but no prior bleeding complications or known bleeding disorders, there was no cause for concern.

• However, parents later mentioned “oozing” with past surgeries

• Right after surgery
  • Per mom, vomiting/retching approx. 5 hours post-op

• 1 day post-op
  • Pt presented to the ER with bleeding from left ear and swelling to left side of face and neck.
  • Coags and platelets came back normal/adequate (PT, aPTT, INR, etc)
  • He was discharged
Case presentation

• Once home
  • Bleeding started again and developed facial hematoma that spread

• Admitted
  • Taken back to OR for exploratory exam and found diffuse oozing.
  • Required cauterization and packing w/ topical thrombin and simultaneous platelet infusion
  • Within an hour, a third bleed was initiated from the left ear and he was given 2nd platelet infusion and FFP (fresh frozen plasma).
  • No further bleeding was noted and bruising slowly resolved.
Differential & Testing

- Differential diagnosis
  - Von willebrand disease
  - Platelet function disorder
  - FXIII deficiency
  - Disorders of the fibrinolytic pathway.
  - Chronic thrombocytopenia
    - Given his Noonan syndrome, pt had BMA/Bx that ruled out JMML as a cause
    - Platelet ct 90K - 100K, so most likely not the cause of bleeding
- PT and PTT were normal and fibrinogen, ruling out many other bleeding disorders
- Labs ordered
  - Von willebrand comprehensive panel
  - Thrombin clotting time
  - Factor XIII functional
  - Platelet function assay (PFA)
Results

• **Factor XIII functional**
  • Showed activity of 20% and 2 weeks later a FXIII activity of <10%.
  • Discrepancy of results possibly due to FFP infusion a couple weeks previously (long half-life).

• **Next steps**
  • Genetic testing to determine etiology
    • Mutation on the F13A1 or F13B genes
    • Acquired inhibitor (antibody)
  • Based on history of easy bruising and quite low FXIII activity, this is consistent with mutation causality.
  • Pts. with an acquired/autoimmune FXIII deficiency usually have activity levels >20%.
  • Although, his recent diagnosis of ulcerative colitis causes suspicion for the development of an antibody to FXIII.
Discussion

• Is there a relationship in this case between Noonan syndrome and FXIII deficiency?
  • Remember that the incidence of Noonan is about 1:2500 and FXIII deficiency is about 1:3,000,000

• The probability of having both of these disorders and them being unrelated is quite low.

• The literature does not make mention of FXIII deficiency having any association with Noonan syndrome. This is the first described case.

• FXIII deficiency has a wide phenotypic spectrum, so we’ll just have to wait and see if and how the genotype explains the phenotype!
Summary

• Noonan syndrome is very common, and you will most likely see it as a clinician.
• Among the many other characteristic abnormalities present, keep in mind bleeding disorders.
  • Specifically, platelet function and/or coagulation abnormalities (XI being cited most commonly).
• If preliminary coagulation tests come back normal, then think about FXIII, fibrinolytic pathway, possibly Von Willebrand and platelets.
• Also, do not ignore history of easy bruising!
• Sequence the genome for FXIII, because knowing the causality will determine treatment/prophylaxis.
Acknowledgments

• Michelle Marcincuk, MD
  • Department of Otolaryngology, Cook Children’s Medical Center

• Marcela Torres, MD
  • Department of Hematology & Oncology, Cook Children’s Medical Center

• W. Paul Bowman, MD
  • University of North Texas Health Science Center

• Tyler Hamby, PhD
  • Department of Research Operations, Cook Children’s Medical Center

• Austin Baker, OMS III
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The End