Gray Platelet Syndrome
IgA Deficiency

Nathan McLamb, MD
Blood Banking and Transfusion Medicine Clinical Fellow

Department of Pathology and Immunology
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Learning Objectives

- Discuss an interesting and complex case in a pregnant patient
- Discuss pathophysiology of Gray Platelet Syndrome
- Discuss pathophysiology of IgA Deficiency
- Discuss preparation strategy for management
- Discuss complications and barriers to management
- Discuss eventual outcome for the patient and newborn

I have no disclosures.

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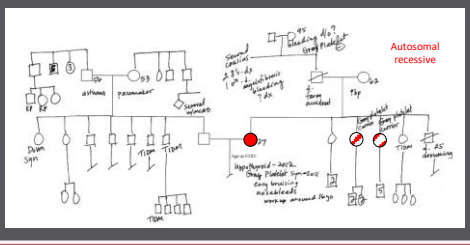
Timeline

Prenatal Consult

10/11/2021

Patient's Family Pedigree



Patient's Genetic Testing

From 2011 at age 17

Clinic *for* Special Children

TARGETED TESTING FOR KNOWN PATHOGENIC VARIANTS IN THE *NBEAL2* GENE CAUSING GRAY PLATELET SYNDROME

Pathogenic sequence variant	p.variant	Result
NBEAL2 c.881C>G	p.Ser294*	Mutation homozygote

Patient:

Homozygous for mutation (gg)

NBEAL2 c.881>G
p.Ser294*

Nonsense mutation

Known AR behavior

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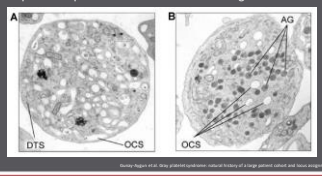
Gray Platelet Syndrome

- Rare congenital bleeding disorder, first described in 1979
  - Also known as α-storage pool disease
  - Quantitative and qualitative platelet defect due to a lack of α-granules

A. GPS Platelet



B. Normal Platelet

AG: α-granules
OCS: Open canalicular system
DTS: Dense tubular system

Gunay-Aygun et al. Gray platelet syndrome: natural history of a large patient cohort and locus assignment to chromosome 3p. Blood. 2010 Dec 2;116(22):4990-5001.

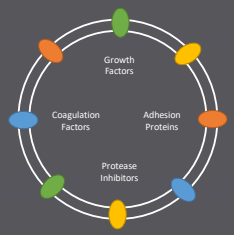
α-Granules

α-Granule

GTP binding proteins:
- rab4, rab6, rab8, Rap1*

Receptors and antigens:
- P-selectin (CD62)
- GPIIbIIIa*
- GPIb-IX*
- GPIV (CD36)*
- p24 (CD9)*
- PECAM (CD 31)*
- GLUT-3
- Vitronectin receptor

Osteonectin
GMP33



α-Granule
Adhesion and repairing factors*

Proteoglycans:
- Platelet specific: βTG, PF4
- Serglycin, HRGP
- βTG Ag molecules: PBP, CTAP-III, NAP-2

Adhesive glycoproteins:
- Fibronectin, Vitronectin, vWF, Thrombospondin

Haemostasis factors and cofactors:
- Fibrinogen, Factor V, VII, XI, XIII
- Kininogens, Protein S, Plasminogen

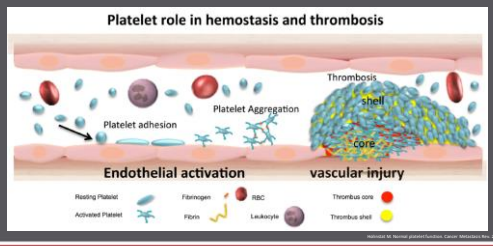
Cellular mitogens:
- PDGF, TGFβ, ECGF, EGF, VEGF/ VPF, IGF, interleukin-β

Protease inhibitors:
- α_2-macroglobulin, α_2-antitrypsin, PDCI
- α_2-antiplasmin, PAI1, TFPI, α_1-PI, PKI
- PN-2/APP, C1 inhibitor

Miscellaneous:
- Immunoglobulins: IgG, IgA, IgM
- Albumin, GPIIa/Multimerin

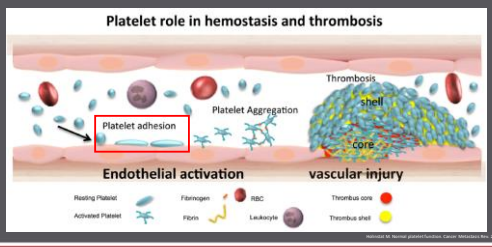
Rendu F and Brohard-Bohn B. The platelet release reaction: granules' constituents, secretion and functions. Platelets. 2001 Aug;12(5):261-73.

α-Granule Function



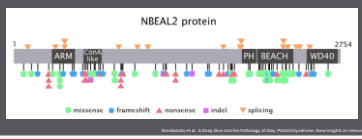
Nishibori M. Normal platelet function. Cancer Metastasis Rev. 2017 Jun;36(2):195-198.

α-Granule Function



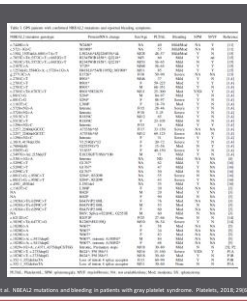
Gray Platelet Syndrome Gene Mutation

- Caused by mutations in NBEAL2, Neurobeachin-like 2
  - Located on chromosome 3p21
  - 86 different mutations in 69 gray platelet syndrome pedigrees as of 2021
  - Usually displays either AR or AD inheritance
    - Some sex-linked variants have been reported



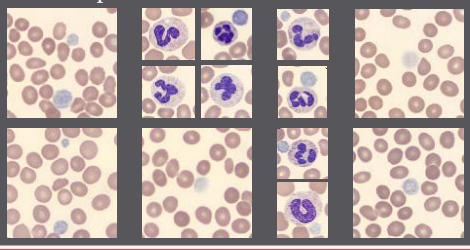
Gray Platelet Syndrome

- Ages: 5 – 68
- M: 21, F: 23
  - M:F Ratio: 0.91
- Platelets: 5 – 351
  - Average: 54
- Bleeding: None – Severe
- Splenomegaly: Yes – 27, No – 11
- Myelofibrosis: Yes – 10, No - 20



F. G. Platero et al. NBEAL2 mutations and bleeding in patients with gray platelet syndrome. Platelets, 2018;29(6):632-635.

Patient's Peripheral Smear



Timeline

Prenatal Consult
10/17/2021
09/19/2022
Establish OB Care
9w0d

Timeline

17w1d
Bleeding Event w/ Transfusion
07/16/2022
Prenatal Consult
10/17/2021
09/19/2022
Establish OB Care
9w0d

Bleeding Event – 07/16/2022

Ultrasound: Concern for large retroplacental and subchorionic hemorrhage

14:41		18:46		
Hemoglobin: 10.6 g/dL Hematocrit: 31.0% Platelets: 67,000/cumm	→	Hemoglobin: 7.7 g/dL Hematocrit: 22.5% Platelets: 56,000/cumm	→	Platelets and packed red blood cells ordered

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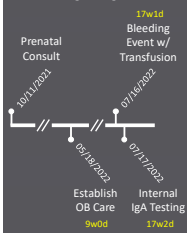
20:30		20:55		
PLT Started HR: 77 SpO2: 99%	→	PLT Stopped HR: 127 SpO2: 84%	→	Flushing Hives SOB Tachycardia Chest Pain Throat tightness

Timeline



IgA Testing – 07/17/2022

Component	Ref Range & Units	6 mo ago
Immunoglobulin A	70.0 - 400.0 mg/dL	<50.0 ↓
Resulting Agency		BJH

- Result: < 50 mg/dL (RR: 70.0 – 400.0 mg/dL)
- Method: Immunoturbidimetric
- Manufacturer: Tina-quant IgA, Roche Corporation. 07/2015.

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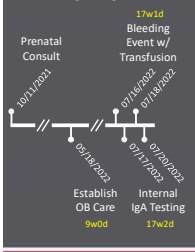
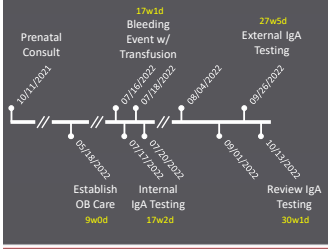
Recommending washed products.

Timeline



Timeline



Reference Lab IgA Testing

SEROLOGY RESULTS

Immunoglobulin A (IgA) Low Range
Eurofins Viracor Accession No:
Performed at: Eurofins Viracor, 18000 W. 99th Street, Lenexa, KS 66219, CLIA # 26D 0959963
Client Accession ID:
Collected:
Final - Approved 10/07/2022 18:04

TEST	RESULT	FLAG	UNITS	REF RANGE
Immunoglobulin A (IgA) Low Range	<0.1	L	mg/dL	72-321

IgA deficiency is indicated if the IgA level is <7mg/dL for adults. Selective IgA deficiency is the most common primary immunodeficiency, occuring in an estimated 1 in 600 individuals. Patients with IgA deficiency may develop antibodies against IgA.

Test	Result	Flag	Unit	Ref Value
Anti-IgA	111	H	U/mL	<99

Patients with IgG antibodies against IgA may suffer from anaphylactoid reactions when given IVIG that contains small quantities of IgA. In one study (Clinical Immunology 2007;122:164) five out of eight patients with IgG anti-IgA antibodies developed anaphylactoid reactions when IVIG was administered. *This test was developed and its performance characteristics determined by Eurofins Viracor. It has not been cleared or approved by the U.S. Food and Drug Administration.

Test Performed by:
Eurofins Viracor
18000 W. 99th Street
Lenexa, KS 66219

IgA Level Result: < 0.1 mg/dL (RR: 72 – 321 mg/dL)

Anti-IgA Result: 111 U/mL (RR: < 99 U/mL)

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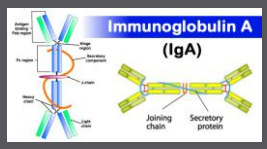
Selective IgA Deficiency

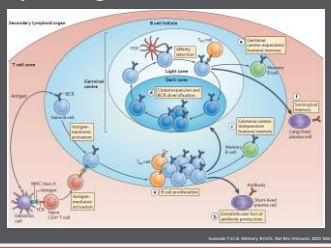
- Most common primary antibody deficiency
- Most people are asymptomatic, but some can have complications, such as:
  - Pulmonary infections
  - Allergies
  - Autoimmune diseases
  - Gastrointestinal disorders
  - Malignancy



Vassilev R K Review. IgA anaphylactic transfusion reactions. Part I. Laboratory diagnosis, incidence, and supply of IgA-deficient products. Immunohematology. 2008;24(4):219-35.

Selective IgA Deficiency Pathogenesis

- Pathogenesis still unknown.
- Some known mutations
- No specific treatments



Kurosaki T et al. Memory B Cells. Nat Rev Immunol. 2015 Mar;15(3):149-59.

Selective IgA Deficiency Diagnosis

- Diagnosis:
  - Age > 4 years
  - IgA levels < 7 mg/dL (our patient < 0.1 mg/dL)
  - Normal IgG and IgM levels
  - Normal IgG response to all vaccinations
  - Exclude:
    - Other causes of hypogammaglobinemia
    - T-cell defects
- Severe deficiency:
  - Variously described as:
    - < 0.5 mg/dL, < 0.16 mg/dL, or 0.05 mg/dL (our patient < 0.1 mg/dL)

Vassilev R K Review. IgA anaphylactic transfusion reactions. Part I. Laboratory diagnosis, incidence, and supply of IgA-deficient products. Immunohematology. 2008;24(4):219-35.

Selective IgA Deficiency and Transfusions

- IgA is naturally found in plasma
- Minor amounts of plasma can be found in most blood products
- Approximately 2.4% of patients with anti-IgA experience major allergic reactions to blood products
- Solutions:
  - Washing products – pRBCs and platelets
  - Deglycerolization – Frozen pRBCs
  - IgA deficient donors – pRBCs, platelets, plasma, other products
    - IgA deficient cryoprecipitate is generally not available

Vassallo R R. Review: IgA anaphylactic transfusion reactions. Part I: Laboratory diagnosis, incidence, and supply of IgA-deficient products. Immunohematology. 2008;24(4):219-35.

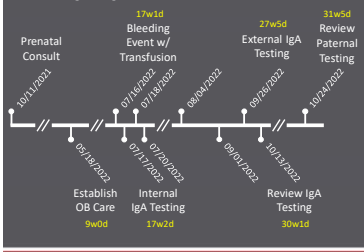
Data from the American Rare Donor Program

- 3 Blood centers actively screening for IgA deficient donors:
  - IgA deficient donors have an IgA < 0.05 mg/dL
  - Approximately 100 active IgA deficient donors
  - Approximately 2200 donors screened in the last year
  - New IgA deficient donors in the last 4 years:
    - Identified: 63
    - Confirmed: 33

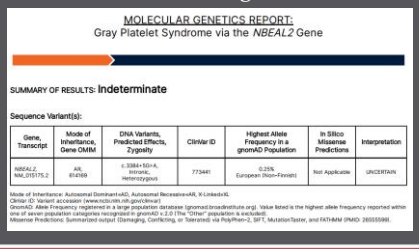
- Frozen IgA Deficient Plasma:
  - A: 112
  - O: 98
  - B: 3
  - AB: 1

Rare Donor Program Slide. Courtesy of Dr. Uzberg

Timeline



Paternal Genetic Testing



MOLECULAR GENETICS REPORT:
Gray Platelet Syndrome via the *NBEAL2* Gene

SUMMARY OF RESULTS: **Indeterminate**

Sequence Variant(s):

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
NBEAL2, NM_015175.2	AR; 614169	c.3384+5G>A, Intronic, Heterozygous	773441	0.25% European (Non-Finnish)	Not Applicable	UNCERTAIN

Mode of Inheritance: Autosomal Dominant=AD, Autosomal Recessive=AR, X-Linked=XL
ClinVar ID: Variant accession (www.ncbi.nlm.nih.gov/clinvar)
GnomAD: Allele Frequency registered in a large population database (gnomad.broadinstitute.org). Value listed is the highest allele frequency reported within one of seven population categories recognized in gnomAD v.2.0 (The "Other" population is excluded).
Missense Predictions: Summarized output (Damaging, Conflicting, or Tolerated) via PolyPhen-2, SIFT, MutationTaster, and FATHMM (PMID: 28555988).

Paternal:

Heterozygous (Gg')

NBEAL2
c.3384+5G>A

Splicing mutation

Known AR behavior

Risk Determination

G = Normal NBEAL2

g = NBEAL2 c.881>G

g' = NBEAL2 c.3384+5G>A

Paternal \ Patient	g	g
G	Gg	Gg
g'	gg'	gg'

Risk Determination

G = Normal NBEAL2

g = NBEAL2 c.881>G

g' = NBEAL2 c.3384+5G>A

50% - Carrier for mothers mutation
50% - Heterozygous for both mutations

Risk for Gray Platelet Syndrome?

37	compound heterozygous	c.3384 + 5G>A
		c.596G>A

Paternal \ Patient	g	g
G	Gg	Gg
g'	gg'	gg'

1. Gresbukby et al. A Deep Dive into the Pathology of Gray Platelet Syndrome: New Insights on Immune Dysregulation. J Blood Med. 2021 Aug 20;12:729-732.

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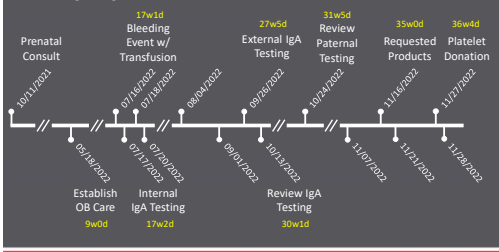

The Plan – Premedication

- 12hrs prior to induction:
  - 50mg PO prednisone
- 1hr prior to transfusions:
  - 50mg PO prednisone
- Prior to transfusions:
  - 650mg PO acetaminophen (Tylenol®)
  - 20mg PO famotidine (Pepcid®)
  - 25mg IV diphenhydramine (Benadryl®)
  - 10mg PO cetirizine (Zyrtec®)

The Plan – Available Blood Products

- Transfuse slowly
- 2 Platelets (pathogen reduced):
  - 1 to be given at start of induction
  - 1 held for use as needed
- 3 Packed red blood cells (+2 frozen):
  - Held for use as needed
- 6 Fresh frozen plasma:
  - Held for use as needed

The Plan – Emergencies

- Controlled bleeding:
  - Volume reduction
  - Washing
  - De-glycerolize frozen products
  - Pre-medicate
- Uncontrolled bleeding:
  - Give general inventory
  - Pre-medicate
  - Prepare for anaphylaxis

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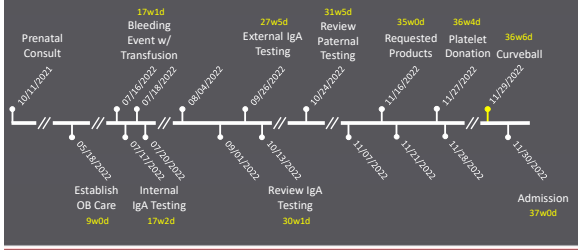

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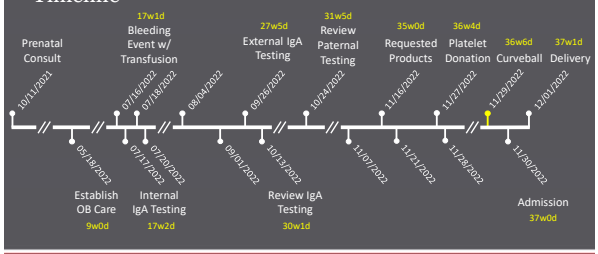
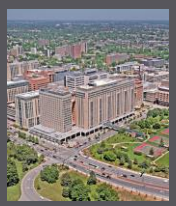


Summary

- Gray Platelet Syndrome
  - Both a qualitative and quantitative platelet disorder
  - Due to a lack of α-granules
  - Occurs from mutations in NBEAL2
- Selective IgA Deficiency
  - Very heterogeneous presentation and severity
  - Small chance of developing clinically relevant IgA antibodies
  - Wash or deglycerolize products
- American Rare Donor Program
  - Able to provide IgA deficient products (< 0.05 mg/dL IgA)

Special thanks



- Dr. Brenda Grossman
- Dr. Suzie Thibodeaux
- Dr. Ron Jackups
- Dr. George Despotis
- Dr. Charles Eby
- Dr. Chang Liu
- Dr. Mei San Tang

- Dr. Cedric Bailey
- Dr. Francesca Vacca
- Dr. Homa Weli
- Cindy Ingold
- Linda Huckelberry
- All the staff in the BJH and SLCH Blood Bank
- All the staff at the American Red Cross
- All the staff at the American Rare Donor Program
- Last, but not least, our unknown rare donor who donated over the holidays.

Nathan McLamb, MD
Blood Banking and Transfusion Medicine Clinical Fellow
Campus Box 8118
660 South Euclid Avenue
St. Louis, MO 63110
(314) 699-2982

mclamb@wustl.edu