Gray Platelet Syndrome
IgA Deficiency

Nathan McLamb, MD
Blood Banking and Transfusion Medicine Clinical Fellow

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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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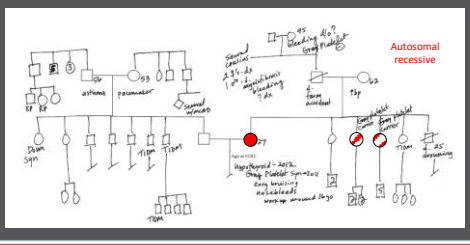
Timeline

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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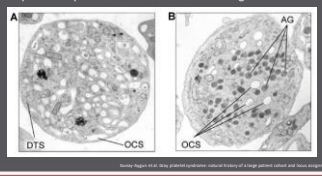
Gray Platelet Syndrome

- 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.

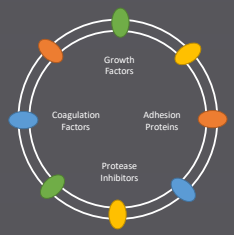
α-Granules

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

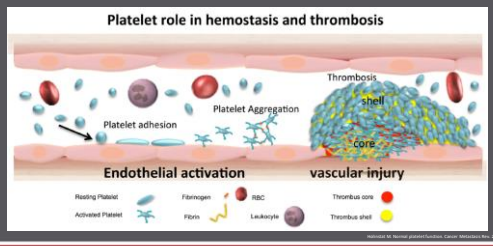
Cellular mitogens:
- PDGF, TGFβ, ECGF, EGF, VEGF/ VPF, IGF, interleukin-β

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

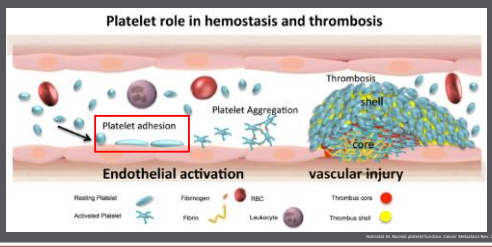
Rendu F and Brohard-Bohn B. The platelet release reaction: granules' constituents, secretion and functions. Platelets. 2001 Aug;12(5):261-73.

α-Granule Function



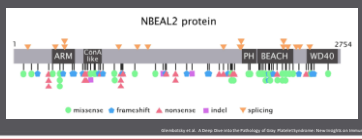
Nishibori M. Normal platelet function. Cancer Metastasis Rev. 2017 Jun;36(2):195-198.

α-Granule Function



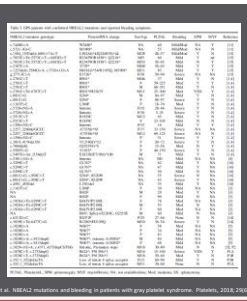
Gray Platelet Syndrome Gene Mutation

- 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



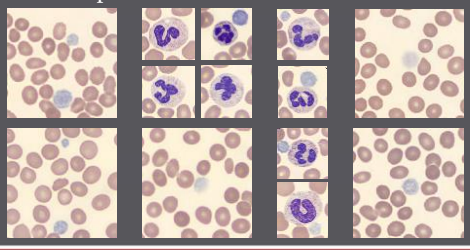
Gray Platelet Syndrome

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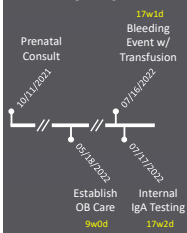
20:30		20:55		
PLT Started HR: 77 SpO2: 99%	→	PLT Stopped HR: 127 SpO2: 84%	→	Flushing Hives SOB Tachycardia Chest Pain Throat tightness

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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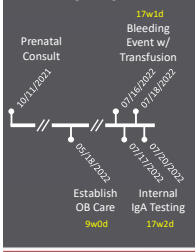
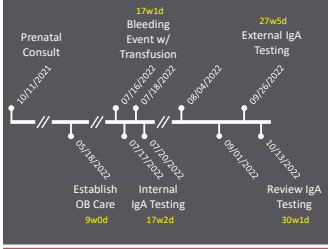
Recommending washed products.

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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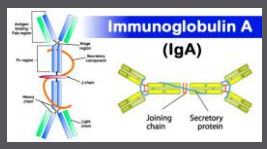
Selective IgA Deficiency

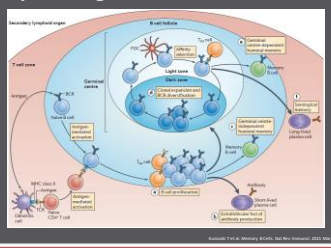
- Most common primary antibody deficiency
- Most people are asymptomatic, but some can have complications, such as:
  - Pulmonary infections
  - Allergies
  - Autoimmune diseases
  - Gastrointestinal disorders
  - Malignancy



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.

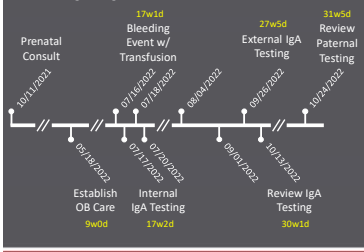
Data from the American Rare Donor Program

- 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

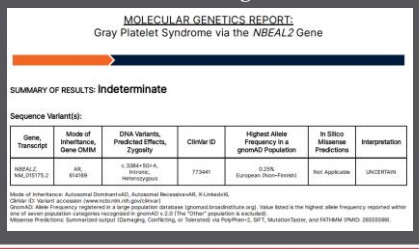
- Frozen IgA Deficient Plasma:
  - A: 112
  - O: 98
  - B: 3
  - AB: 1

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 31;12:759-782.

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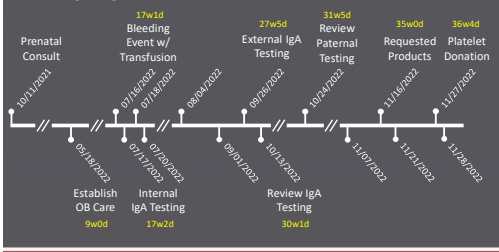

The Plan – Premedication

- 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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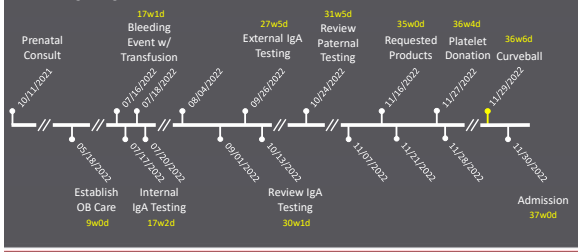

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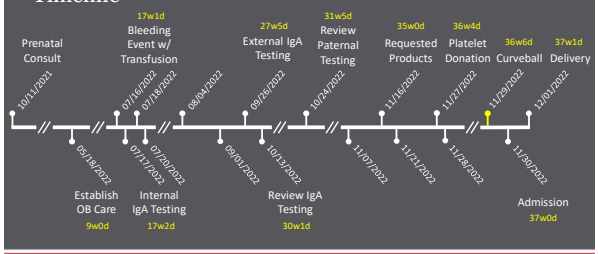
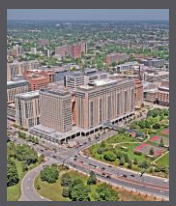


Summary

- 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.

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