PROTEIN S DEFICIENCY: A SYSTEMATIC CASE REVIEW

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DISCLOSURE

NO ONE PAYS ME TO SELL
OR PROMOTE THINGS

"Actually, I'm an athletic trainer. I just do hair removal on the side."

OBJECTIVES

- SUMMARIZE WHAT IS PROTEIN S DEFICIENCY AND THE ACCOMMODATIONS THAT AN ATHLETE WITH THIS CONDITION MAY HAVE
- EXPLAIN THE RISKS FOR AN ATHLETE TO BE ON ANTICOAGULANTS
- IDENTIFY A HEREDITARY VS ACQUIRED RISK OF THROMBOPHILIA
- DESIGN A COMMUNICATION POLICY FOR WORKING WITH ATHLETES, COACHES, TEACHERS, AND ADMINISTRATORS ABOUT ATHLETES WITH SPECIAL CONDITIONS
- DETERMINE A RETURN TO SPORT PROTOCOL FOR AN ATHLETE WITH A PROTEIN S DEFICIENCY

DEFINITIONS

- **COAGULATION** (ALSO KNOWN AS **CLOTTING**)
  - IS THE **PROCESS** BY WHICH **BLOOD** CHANGES FROM A LIQUID TO A GEL, FORMING A **CLOT**. IT POTENTIALLY RESULTS IN HEMOSTASIS, THE CESSATION OF **BLOOD** LOSS FROM A DAMAGED VESSEL, FOLLOWED BY REPAIR.
- **HYPERCOAGULABILITY**
  - A POTENTIALLY DANGEROUS CONDITION IN WHICH BLOOD COAGULATES EXCESSIVELY, EVEN WITHIN THE BLOOD VESSELS

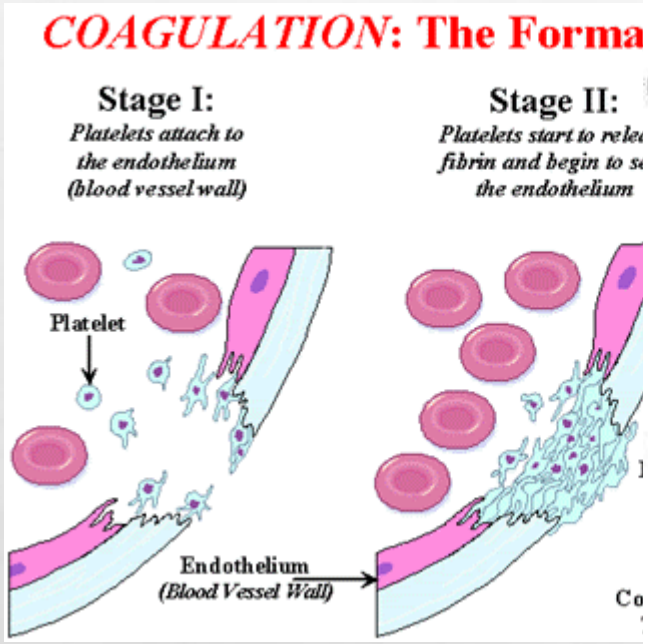
DEFINITIONS

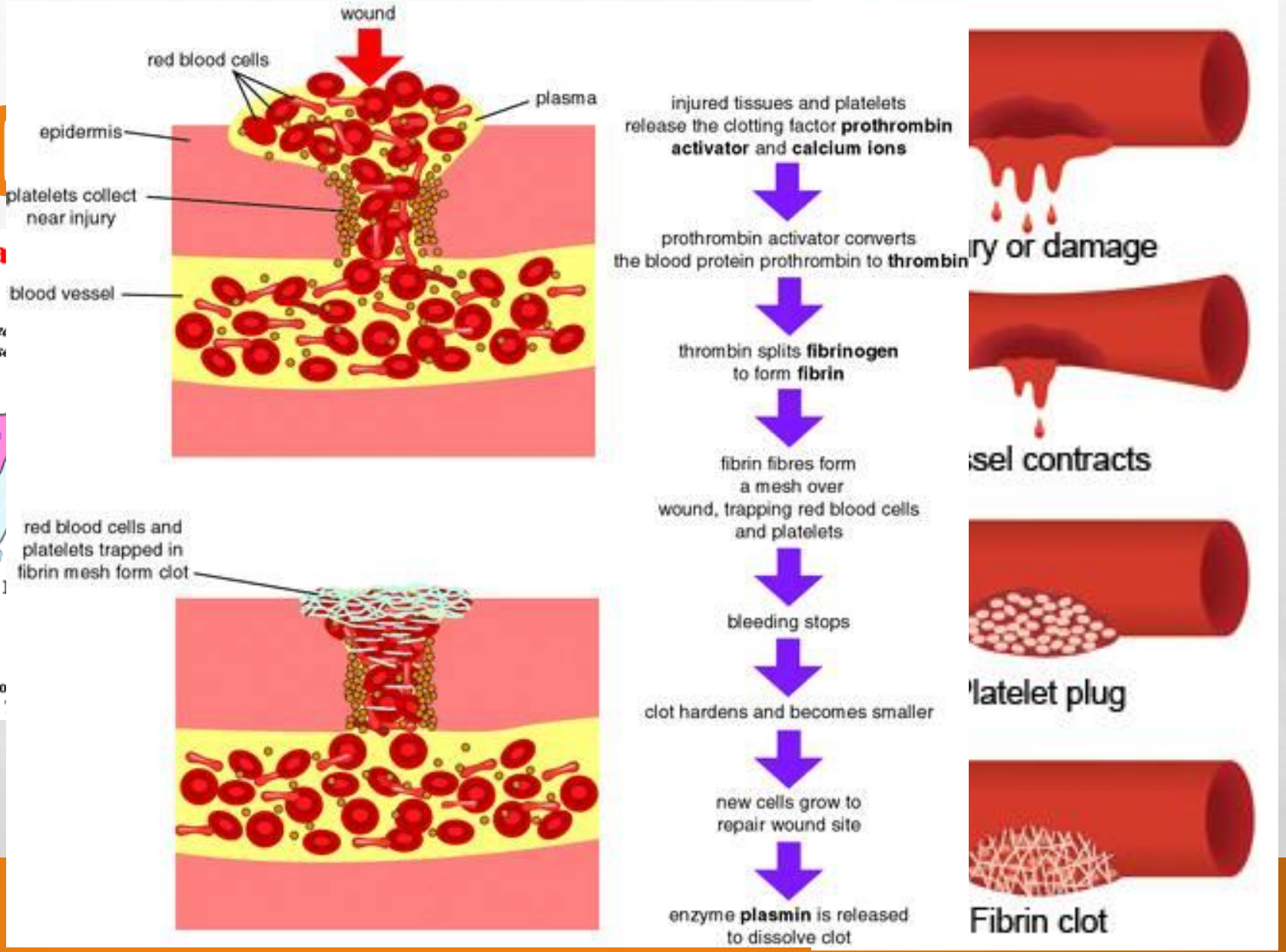
- **THROMBOSIS**
  - LOCAL COAGULATION OR CLOTTING OF THE BLOOD IN A PART OF THE CIRCULATORY SYSTEM.
- **THROMBOPHILIA**
  - THROMBOPHILIA IS AN ABNORMALITY OF BLOOD COAGULATION THAT INCREASES THE RISK OF THROMBOSIS. SUCH ABNORMALITIES CAN BE IDENTIFIED IN 50% OF PEOPLE WHO HAVE AN EPISODE OF THROMBOSIS THAT WAS NOT PROVOKED BY OTHER CAUSES. A SIGNIFICANT PROPORTION OF THE POPULATION HAS A DETECTABLE ABNORMALITY, BUT MOST OF THESE ONLY DEVELOP THROMBOSIS IN THE PRESENCE OF AN ADDITIONAL RISK FACTOR.

BASIC SCIENCE

- COAGULATION CASCADE IS A SERIES OF ENZYMATIC CONVERSIONS CULMINATING IN THE FORMATION OF THROMBIN → CONVERTS TO FIBRINOGEN → FIBRIN TO CREATE A HEMOSTATIC PLUG
- INTRINSIC AND EXTRINSIC PATHWAYS SEPARATED BY FACTOR X
- PATHWAY MUST BE RESTRICTED TO THE LOCAL AREA TO PREVENT CLOTTING OF THE ENTIRE VASCULAR SYSTEM BY ANTICOAGULANT FACTORS
- PRIMARY INFLUENCES: ENDOTHELIAL INJURY, ABNORMAL BLOOD FLOW & HYPERCOAGULABILITY

BLOOD CLO

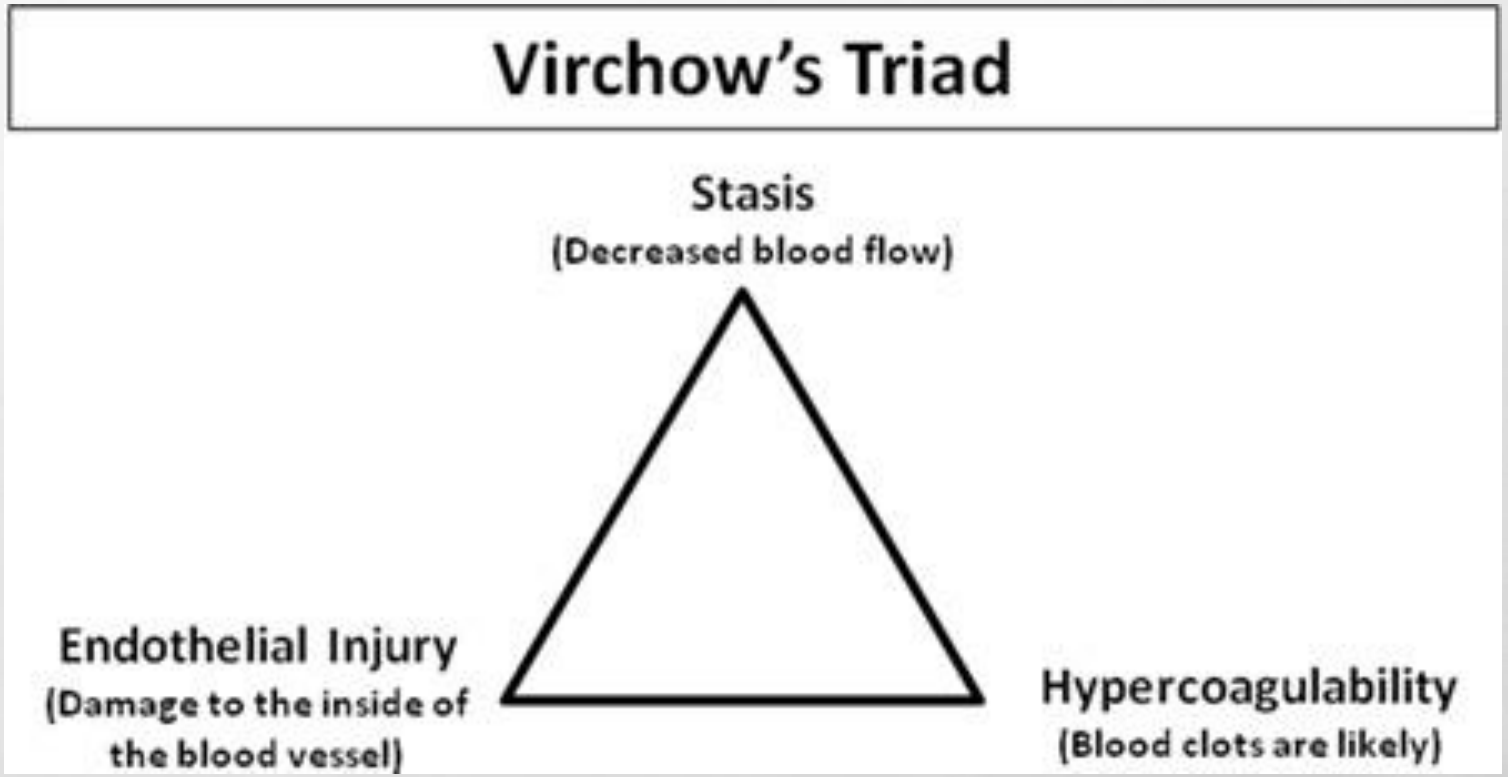




HOW DOES THE BLOOD CLOT?

RISKS OF THROMBOPHILIA

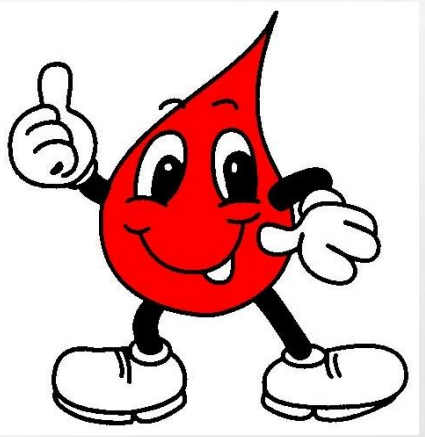
- GENERAL POPULATION → VENOUS THROMBOSIS OCCURS IN 1 OF 1000
- **VIRCHOW'S TRIAD** DESCRIBES THE THREE BROAD CATEGORIES OF FACTORS THAT ARE THOUGHT TO CONTRIBUTE TO THROMBOSIS.



CONDITIONS ASSOCIATED WITH AN INCREASED RISK OF THROMBOSIS

- INHERITED
  - FACTOR V LEIDEN MUTATION
  - ANTITHROMBIN III DEFICIENCY
  - PROTEIN C DEFICIENCY
  - PROTEIN S DEFICIENCY
  - PROTHROMMBIN G20210A MUTATION
- ACQUIRED
  - IMMOBILIZATION
  - TISSUE DAMAGE
  - MALIGNANCY
  - ORAL CONTRACEPTIVE USE
  - OBESITY
  - ADVANCED AGE (> 60 YEARS)
  - PREGNANCY
  - ANTIPHOPHOLID SYNDROME

HEREDITARY RISK FACTORS

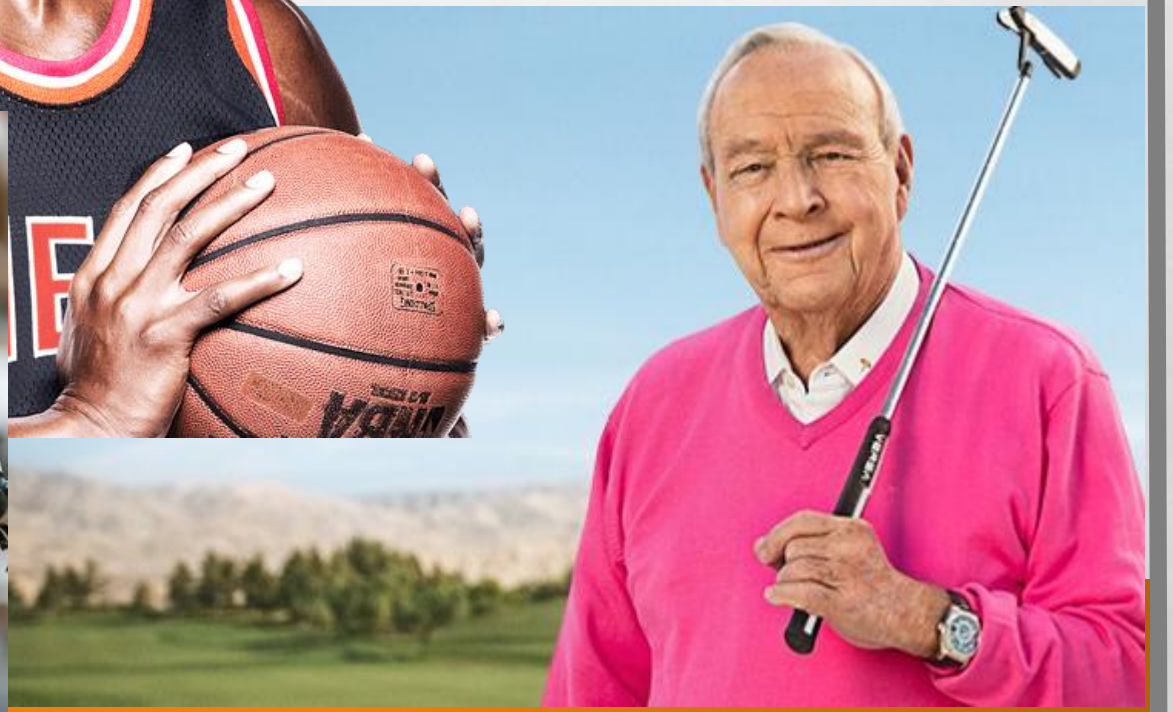


- CAUSE THE BALANCE BETWEEN PROCOAGULANT AND ANTICOAGULANT ACTIVITY TO BE TIPPED IN FAVOR OF THROMBUS FORMATION BY OVERACTIVE COAGULOPAHTIC FACTORS OR UNDERACTICE ANTITHROMBOTIC FACTORS
- MOST COMMON HYPERACTIVITY OF COAGULATION FACTORS : FACTOR V LEIDEN AND PROTHROMBIN G20210A = NO CLOT
- HYPOACTIVIY OF ANTITHROMBIC PATHWAYS: ANTITHROMBIN III DEFICIENCY, PROTEIN C DEFICIENCY AND PROTEIN S DEFICIENCY = CLOT FORMED

STATISTICS

- LIFETIME PROBABILITY OF DEVELOPING THROMBOSIS:
  - 8.5 TIMES HIGHER FOR CARRIERS OF PROTEIN S DEFICIENCY
  - 8.1 TIMES HIGHER FOR ANTITHROMBIN DEFICIENCY
  - 7.3 TIMES HIGHER FOR PROTEIN C DEFICIENCY
  - 2.2 TIMES HIGHER FOR FACTOR V LEIDEN MUTATION
- 15% OF PATIENTS WHO PRESENTS WITH A VT BEFORE AGE 45 HAVE BEEN SHOWN TO HAVE A DEFICIENCY OF PROTEIN C, PROTEIN S OR ANTITHROMBIN III.
- PEOPLE WITH HEREDITARY DEFICIENCY (C OR S) HAVE APPROXIMATELY 2 TO 11 FOLD INCREASED RISK OF DEVELOPING A DVT

CASE EXAMPLE



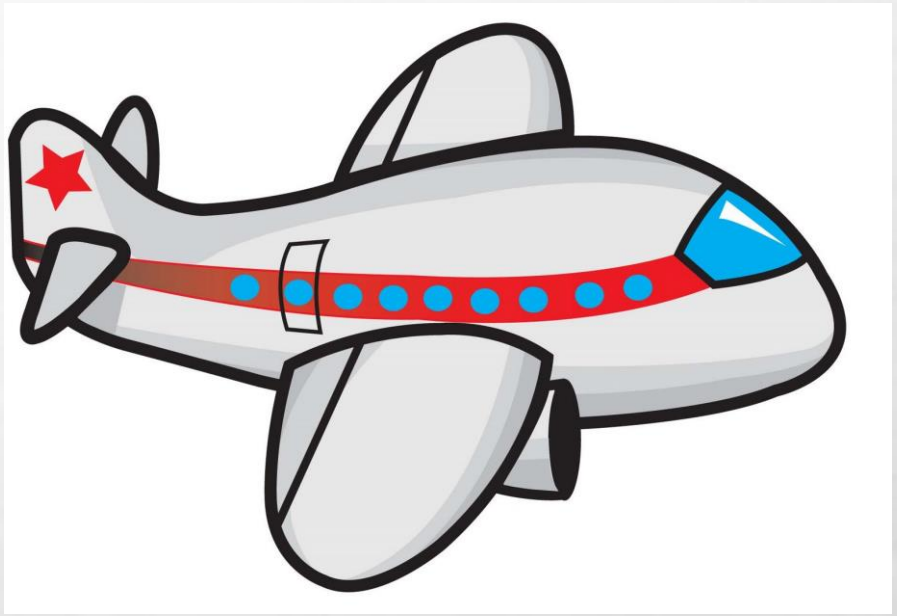
AUGUST 2011

- 13 YEAR OLD FEMALE
- OLDEST OF 5 CHILDREN
- EVENING BEFORE THE CROW FAIR – NECK PAIN/ NUMBNESS/ REMEDY OF A MASSAGE/ SYMPTOMS DISAPPEARED

SEPTEMBER 2011

- MONDAY – AT SCHOOL – CALLS MOM WITH A HEADACHE & DIZZINESS – GO TO THE ED & DIAGNOSED WITH MIGRAINES – ELEVATED BP – GIVEN NSAIDS AND TOLD TO SLEEP
- TUESDAY – BACK TO ED – TOLD NURSE “I HAVE A TUMOR IN MY HEAD”, DOCTOR ORDERS A CT SCAN AND REVEALS AN ENLARGED VESSEL IN THE HEAD – SCHEDULE AN MRI FOR TOMORROW
- 2AM WEDNESDAY – UNCONTROLLED VOMITING – DRIVE 16 MILES TO TOWN TO ED
  - “I’M DYING”
  - “IF NOT FOR MY HEAD FROM A CAR ACCIDENT”

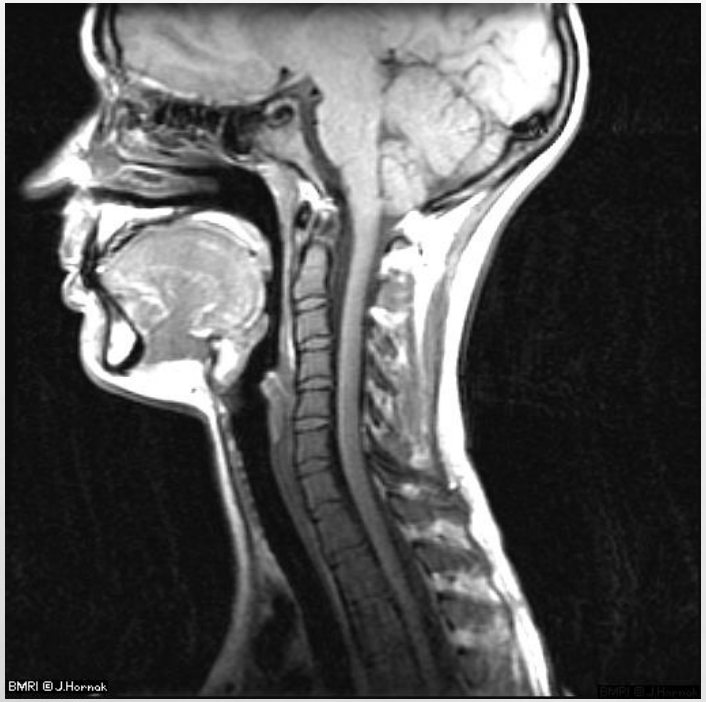
- ADMITTED TO THE ED WITH S/S: LOSING VISION, UNABLE TO CONTROL BODY, ELEVATED BP
- SEDATED
- WOKE UP IN MRI & IS CLAUSTROPHOBIC – VALIUM
- WOKE UP BEING STRAPPED INTO AMBULANCE TO FLY TO DENVER
- MOM “ FEELS LIKE A BAD DREAM”

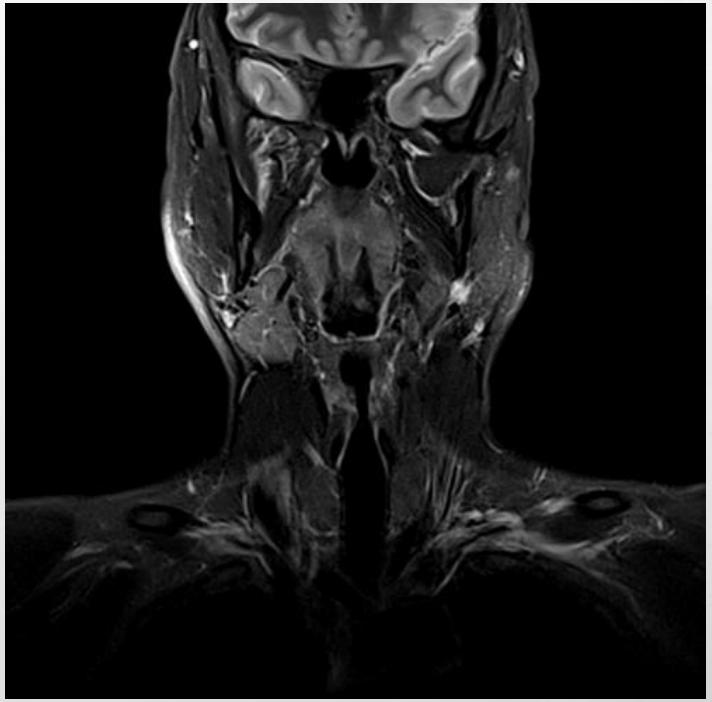


DENVER

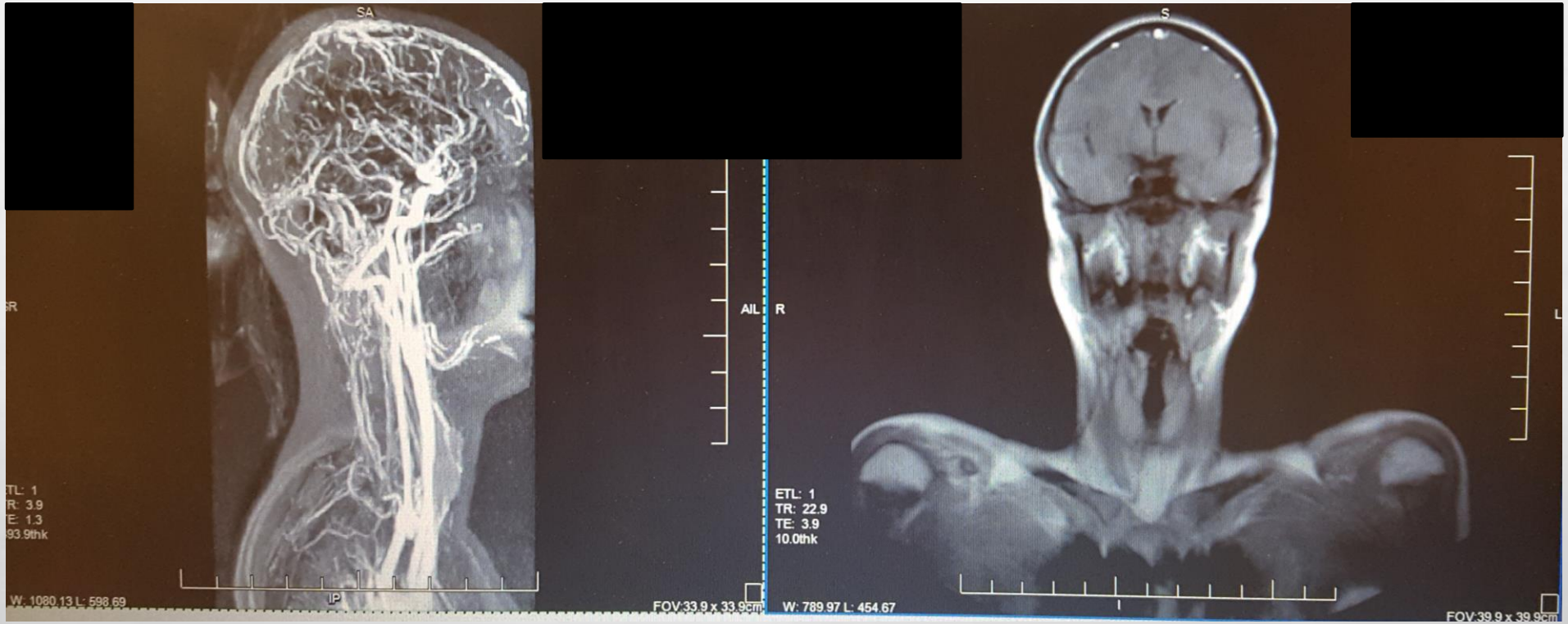
- SUPPORT SYSTEM OF FAMILY – MOM AND DAD STAY WITH HER THE ENTIRE TIME
- GIVEN ANTICOAGULANTS (BLOOD THINNERS)
- DOCTORS SAY “YOU SHOULD BE DEAD”

NORMAL MRI OF THE NECK





PATIENT'S MRI



DENVER

- GIVEN A CEREBRAL SPINAL FLUID REDUCER TO DECREASE BP – MESSED WITH EQUILIBRIUM – COULD NOT BALANCE
- SPEECH – “4 YEAR OLD BROTHER”
- STRUGGLED GOING TO THE RESTROOM (MOM HELPED)
- REFUSED TO SHOWER
- VERY PAINFUL – MORPHINE AND FENTANYL PATCHES
- BLOOD DRAWN 3 TIMES A DAY
- LOVENOX SHOTS

DENVER

- MEDICAL TEAM: STROKE TEAM, PAIN TEAM, PSYCHOLOGIST, BLOOD DOCTOR
- STROKE TEST – 3 TIMES A DAY
- REPEAT MRI AND DECREASED BLOOD CLOT
- DISCHARGED AFTER 15 DAYS BUT NO SPORTS DUE TO BLOOD THINNERS
  - DEPRESSION & “PISSED”

HOME

- SLEPT IN A HOSPITAL BED IN HER HOUSE TO BE ELEVATED – GRAVITY
- LOVENOX SHOTS – 2 TIMES PER DAY
  - SELF ADMINISTERED
  - CAUSED BRUISES, STARTED IN STOMACH THEN TO LEGS AND TO ARMS

3 MONTH FOLLOW - UP IN DENVER

- “NO CLOT!!” BUT STILL NO SPORTS
- SWITCHED TO WARFARIN 1 TIME PER DAY
- PLAYED VOLLEYBALL ANYWAYS – BRUISED HER ARMS

6 MONTH FOLLOW- UP DENVER

- NO BLOOD THINNER
- SIDE-AFFECT : PERIPHERAL VISION ON LEFT SIDE AFFECTED
- RETURNED TO SCHOOL WITH 1 WEEK LEFT OF HER 8TH GRADE YEAR
- CLEARED FOR SPORTS
- DIAGNOSED WITH PROTEIN S DEFICIENCY

WHAT IS PROTEIN S DEFICIENCY?

- DISCOVERED IN 1984 – INHERITED THROMBOPHILIA
- FOUND IN LESS <2% OF GENERAL POPULATION
- AUTOSOMAL DOMINANT TRAIT THAT EITHER DECREASES THE LEVELS OF PROTEIN S OR DECREASES ITS FUNCTION
- WORKS CLOSELY WITH PROTEIN C TO LIMIT THROMBIN ACTIVATION
- BREAKS UP CLOTS AND IF LOW THEN CLOTS CAN FORM

Normal Protein S level is 50%
Patient initial diagnoses was 10% and now she is at 40%

POSSIBLE CAUSES

- BOTH PARENTS HAD GENETIC TESTING DONE AND NEGATIVE FOR BEING CARRIERS OF PASSING PROTEIN S DEFICIENCY TO PATIENT
  - ALL SIBLINGS WERE TESTED AND THEY ARE NEGATIVE
- OTHER ACQUIRED RISK FACTORS- ORAL CONTRACEPTIVE USE

- ACQUIRED
  - ~~IMMOBILIZATION~~
  - ~~TISSUE DAMAGE~~
  - ~~MALIGNANCY~~
  - ORAL CONTRACEPTIVE USE
  - ~~OBESITY~~
  - ~~ADVANCED AGE (> 60 YEARS)~~
  - ~~PREGNANCY~~
  - ~~ANTIPHOPHOLID SYNDROME~~

EXERCISE AND THROMBOGENESIS

- BLOOD LEVELS OF THE CLOTTING PROTEIN FACTOR VIII AND OTHER PROTHROMBOTIC MARKERS INCREASE WITH EXERCISES
  - PROTEIN S INACTIVATES THIS PROCESS TO BREAK UP/STOP THROMBIN FORMATION
- HOMEOSTASIS CAN BE DISRUPTED BY STRENUOUS EXERCISE ALONE
  - CONCLUDED THAT MODERATION AND CONSISTENCY MAY BE A BETTER WAY TO MAINTAIN HOMEOSTASIS BETWEEN THROMBOSIS AND FIBRINOLYSIS THAN STRENUOUS EXERCISE ALONE
- EXERCISE AND HEREDITARY THROMBOPHILIA MAY PLACE PREDISPOSED ATHLETES AT FURTHER RISK OF VENOUS THROMBOSIS

So do you exercise of not?

RETURN TO ACTIVITY - SCREENING

- ACADEMY OF ORTHOPAEDIC SURGEONS
- PPES – PATIENTS SHOULD BE ASKED REGARDING HIGH-ALTITUDE TRAINING OR SIMULATION AND DRUG USE IN ADDITION TO PERSONAL AND FAMILY HISTORY OF VTE

RETURN TO ACTIVITY - PREVENTION

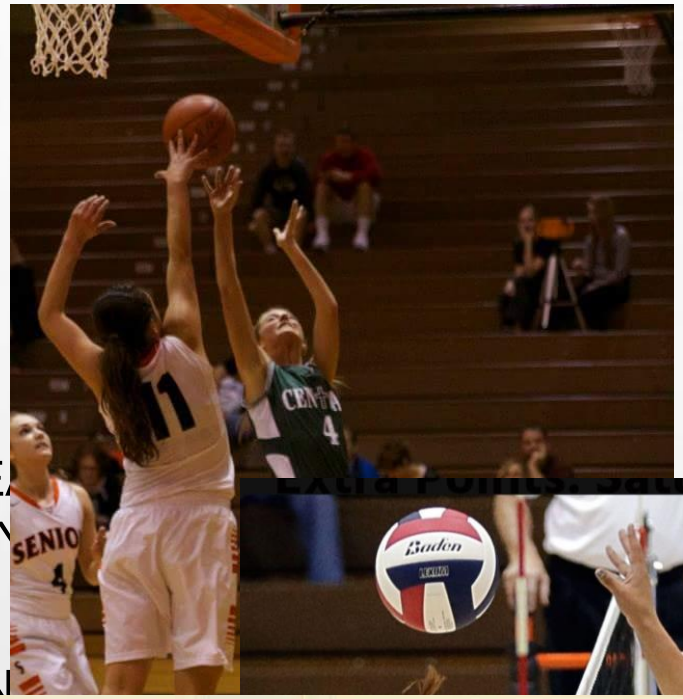
- RECOMMEND CONSIDERING ANTICOAGULANT ALONG WITH PHYSICAL ANTITHROMOTIC MEASURES IN ATHLETES WHO ARE IMMOBILIZED DUE TO TRAUMA/ SURGERY/ILLNESS

RETURN TO ACTIVITY - MANAGEMENT

- GRADUAL RETURN TO ACTIVITIES OF DAILY LIVING THE DAY THEY BEGIN ANTICOAGULATION THERAPY
- STRUCTURED RETURN TO TRAINING PROGRAM WITH PROGRESSIVE INCREASE IN INTENSITY AFTER ADL MASTERY
- MONITOR CAREFULLY FOR RECURRENCE OF DVT
- NO CONTACT OR COLLISION SPORTS UNTIL ANTICOAGULATION THERAPY IS COMPLETE
- MOST WHO SUFFER A DVT DO NOT RETURN TO COLLISION SPORTS DUE TO A INCREASED RATE OF REOCCURRENCE

FUTURE

- POST DVT – PLAYED 4 YE
  AND BASKETBALL AND 2 Y
  TRACK
- 6 MONTH APTS WITH DEN
  FR AND SO YEARS. NO
  NEEDS FOLLOW-UPS
- SIGNED TO PLAY COLL
- WANTS TO BE A PA IN
  FAMILY



QUESTIONS?

RELEASE

May 6th, 2016

I, Naomi Bad Bear and my family, give Stacy Molt permission to tell the story of my medical history of having a Protein S Deficiency and how this diagnoses has impacted my sports involvement. I also give permission for Stacy to use photos of myself.

Stacy is presenting my case to athletic trainers to allow them to better understand athletes with blood conditions.

Naomi Bad Bear

Naomi Bad Bear

5/6/16

Date

REFERENCES

- HILBERG, THOMAS, JESCHKE, DIETER, GABRIEL, & HOLGER. (2002, FEBRUARY). HEREDITARY THROMBOPHILIA IN ELITE ATHLETES. *MEDICINE & SCIENE IN SPORTS & EXERCISE*, *34*(2), 218-221. RETRIEVED FROM PUBMED.
- MARTINELLI, I., BATTAGLIOLI, T., BUCCIARELLI, P., PASSAMONTI, S., & MANNUCCI, P. (2004, AUGUST 3). RISK FACTOS AND RECURRENCE RATE OF PRIMARY DEEP VEIN THROMBOSIS OF THE UPPER EXTREMITIES. *EPUB*, *110*(5), 566-570. RETRIEVED FROM PUBMED.
- KARDIOL, Z., MARZ, W., NAUCK, M., & WEILAND, H. (2000, JULY). THE MOLECULAR MECHANISMS OF INHERITED THROMBOPHILIA. *89*(7), 575-586. RETRIEVED FROM PUBMED.
- JANG, M., KIM, S., KIM, D., & KIM, H. (2015, MARCH). A NOVEL NONSENSE MUTATION TYR301* OF PROS1 CAUSING PROTEIN S DEFICIENCY. *BLOOD COAGUL FIBRINOLYSIS*, *26*(2), 223-224. DOI:10.1097/MBC.0000000000000217
- KHALFALLAH, A., IBRAHEEM, A., TEO, Q., ALBARZAN, A., PARAMSWARAN, R., HOOPER, E., & PAVLOV. (2014, FEBRUARY). REVIEW OF MANAGEMENT AND OUTCOMES IN WOMEN WITH THROMBOPHILIA RISK DURING PREGNANCY AT A SINGLE INSTITUTION. *ISRN OBSTET GYNECOL*. DOI:10.1155/2014/381826
- RICHARD, S., LACOUR, J., FROTSCHER, B., ENEA, A., MIONE, G., & DUCROCQ, X. (2014, SEPTEMBER 22). REPORT OF A RECURRENT CEREBRAL VENOUS THROMBOSIS IN A YOUNG ATHLETE. *BMC NEUROL*. DOI:10.1186/S12883-014-0182-3
- GRABOWSKI, ., GREGORY MD, ., WHITESIDE, ., WILLIAM MD, K., KANWISHER, ., & MICHAEL MD, . (2013, FEBRUARY). VENOUS THROMBOSIS IN ATHLETES. *JOURNAL OF THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS*, *21*(2), 108-117. DOI:DX.DOI.ORG/10.5435/JAAOS-21-02-108
- DEPENBROCK MD, P. J. (2011, MARCH). THROMBOEMBOLIC DISORDERS: GUIDANCE FOR RETURN TO PLAY. *CURRENT SPORTS MEDICINE REPORTS*, *10*(2), 78-83. DOI:10.1249/JSR.0B013E318214D828
- MEYERING, C., & HOWARD, T. (2004, APRIL). HYPERCOAGULABILITY IN ATHLETES. *CURRENT SPORTS MEDICINE REPORTS*, *3*(2), 77-83. RETRIEVED FROM PUBMED.
- RODERICK, P., FERRIS, G., WILSON, K., HALLS, H., JACKSON, D., COLLINS, R., & BAIGENT, C. (2005, DECEMBER). TOWARDS EVIDENCE BASED GUIDELINES FOR PREVENTION OF VENOUS THROMBOEMBOLISM: SYSTEMATIC REVIEWS OF MECHANICAL METHODS, ORAL ANTICOAGULATION, DEXTRAN AND REGIONAL ANAESTHESIA AS THROMBOPROPHYLAXIS. *HEALTH TECHNOL ASSESS*, *9*(49), 1-78. RETRIEVED FROM PUBMED.