

# **ADAMTS13 distinguishes TTP from other thrombotic microangiopathies**



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# Introduction



- **TTP is characterized by MAHA and thrombocytopenia**
- **CNS involvement present in ~60-80%**
- **Renal involvement and fever not present in most patients**
- **Old “pentad” is not helpful in diagnosis**
  - **A “biad” of MAHA and low plt count is sufficient to suspect TTP and initiate PLEX**
- **Mortality rate of ~80% without PLEX, 10-20% with PLEX**

# Introduction



- **MAHA and low plt encountered in clinical conditions other than TTP – Thrombotic Microangiopathy (TMA)**
  - **HUS, aHUS, drugs, SLE, infection, malignancy, malignant hypertension**
- **PLEX is not beneficial for TMA, except for aHUS, due to complement factor defect/deficiency**
- **Distinguishing TTP from TMAs important for long-term care and adjunct therapies**

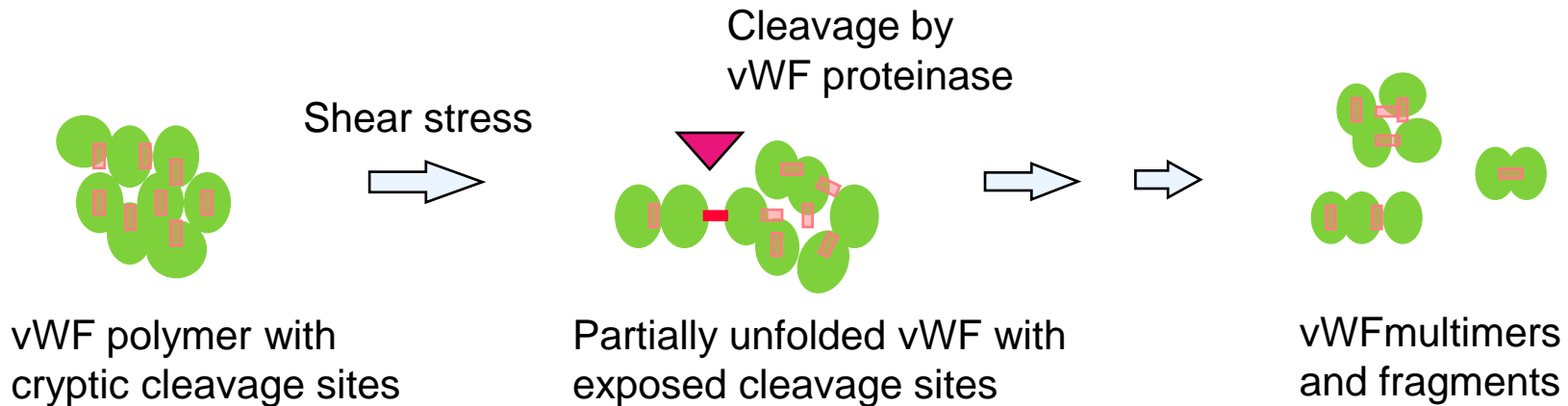
# Congenital TTP = Upshaw-Schulman Syndrome (USS)



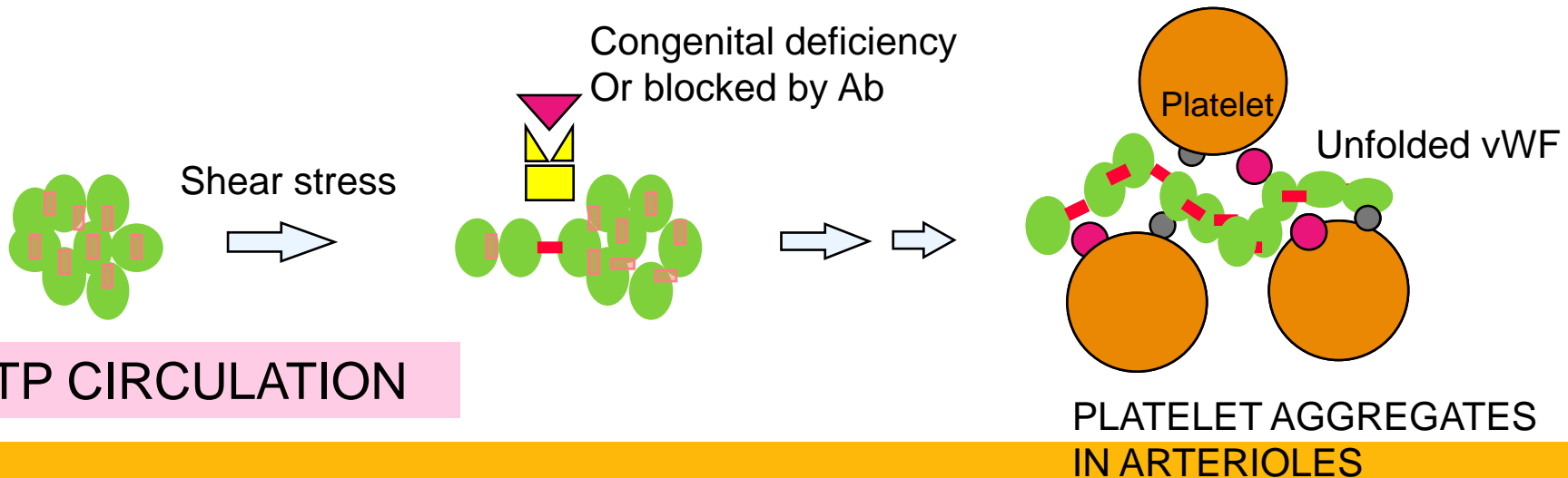
- **USS characterized by genetic defect in ADAMTS13 gene**
  - Increased levels of UL-VWF → platelet aggregation
  - >90 described mutations lead to microthrombi and varied clinical presentation
- **90% of double heterozygote / homozygous mutations in ADAMTS13 gene show TTP phenotype**
- **ADAMTS13 deficient murine models were pro-thrombotic but did not develop TTP**

# A DEFICIENCY OF ADAMTS13 LEADS TO VWF-PLATELET THROMBOSIS

## NORMAL CIRCULATION



## TTP CIRCULATION



# Acquired TTP is Autoimmune



- **Landmark studies (Tsai, Furlan – NEJM 1998) showed severe deficiency of ADAMTS13 in acquired TTP due to auto-antibody**
- **PLEX with “plasma” effective in removing autoAb and replacing enzyme**
- **However, 30-50% TTP exacerbate/relapse without adjunct immunotherapy**
- **ADAMTS13 not widely used in acute clinical decision making in MAHA**

# Defining TTP



- **Timely availability of ADAMTS13**
- **Controversy: does severe ADAMTS13 deficiency define TTP or just serve as a model in some cases**
- **ADAMTS13 levels can be lower in other conditions such as sepsis, DIC, liver failure, etc.**
  - **Possible lower levels but no SEVERE DEFICIENCY**
- **Subset of TTP population with severe ADAMTS13 deficiency, high inhibitor without acute symptoms**
  - **All eventually relapse, sometimes >1yr after**

# ADAMTS13 Test



- **Commercial FRET assay for ADAMTS13 available from The Blood Center of Wisconsin since 2005**
- **FRET assay is rapid, reliable and reproducible with a detection lower limit of 5% activity**
- **Reflex inhibitor assay performed for <30%**
- **Results available expeditiously and interfaced with LIS and EMR**

# Purpose



- **To use severe ADAMTS13 deficiency (<10%) to distinguish TTP from TMA**
- **Analyze patient response to PLEX and overall clinical outcome at a single academic center with a uniform treatment plan**
- **Hematology and transfusion medicine closely collaborate in patient management**

# Treatment Plan



- **Daily PLEX with FFP as replacement fluid**
- **Glucocorticoids – 1mg/kg**
- **If ADAMTS13 <10% continue PLEX, if >20% discontinue**
- **Short PLEX taper for good responders and long taper for poor responders**
- **Rituximab is used as an adjunct**

# Study Design



- **Consecutive chart review of patients with TMA that had ADAMTS13 drawn between January 2006-April 2011 (FRET assay)**
- **Parameters of presenting symptoms, laboratory values, underlying diagnosis [SLE, drugs, malignancy, infection], number of PLEX, steroids and other immunosuppression, response, and relapse**
- **Statistical analysis with unpaired t-test for means and Fisher's exact method for contingency tables**

# Demographics



	<b>TTP</b>	<b>TMA</b>
<b>Total patients</b>	<b>25 (29 episodes)</b>	<b>26</b>
<b>Median Age</b>	<b>40</b>	<b>47</b>
<b>Sex (females %)</b>	<b>72%</b>	<b>58%</b>
<b>PLEX performed</b>	<b>90%</b>	<b>50%</b>
<b>Total PLEX (median)</b>	<b>16</b>	<b>5</b>
<b>Total Inpatient Stay (median days)</b>	<b>9</b>	<b>20</b>
<b>HIV+</b>	<b>23%</b>	<b>39%</b>

- **3 patients in TTP group did not receive PLEX**
  - 1 passed away during central line placement, 1 refused FFP (Jehovah's witness), and 1 was electively started just on steroids by primary team
- **TMA group included:**
  - Malignancy (3), SLE/MCTD (5), HIV (4), drugs (3), infection (3), malignant HTN (1), preeclampsia/HEELP/PP (2), quinine (1), and multiple/other (4)

# Presenting Signs/symptoms



	<b>TTP</b>	<b>TMA</b>	<b>p-value</b>
<b>Fever</b>	<b>28%</b>	<b>19%</b>	<b>0.35</b>
<b>Neurological symptoms</b>	<b>62%</b>	<b>42%</b>	<b>0.18</b>

- **TTP group: headache (9), lightheadedness/dizziness- (7), seizures (1), vision changes(2), speech abnormalities (3), confused/altered- 17% (3)**
- **TMA group: unresponsive (8), seizures (1), blurry vision (1), syncope (1)**

# Presenting Laboratory



	TTP	TMA	p-value
ADAMTS13 activity $\leq$ 10%	100%	0/26 (0%) [mean=55%, 33-122%]	
Platelet count $\times 10^9$ /L (mean $\pm$ SD)	26 $\pm$ 28	66 $\pm$ 40	0.0001
LD units/L (mean $\pm$ SD)	990 $\pm$ 648	1371 $\pm$ 1446	0.2
Hematocrit % (mean $\pm$ SD)	25.9 $\pm$ 7.6	26.9 $\pm$ 5.0	0.57
Creatinine mg/dL (mean $\pm$ SD)	1.34 $\pm$ 0.96	2.5 $\pm$ 2.2	0.0127

# Treatment Response



	<b>TTP</b>	<b>TMA</b>	<b>p-value</b>
<b>Normalization of platelet count (&gt;150 x10<sup>9</sup>/L)</b>	<b>96%</b>	<b>23%</b>	<b>0.0001</b>
<b>LD &lt;338 units/L [1.5 x upper limit of normal]</b>	<b>78%</b>	<b>31%</b>	<b>0.009</b>
<b>Mortality</b>	<b>14%/7%</b>	<b>4.2%</b>	<b>0.355</b>

# Adjunct Therapy



	<b>TTP</b>	<b>TMA</b>
<b>Rituxan</b>	<b>28%</b>	<b>0%</b>
<b>Steroids</b>	<b>97%</b>	<b>65%</b>
<b>Other Immunosuppression</b>	<b>14%</b>	<b>31%</b>

- **TTP**

- Cyclophosphamide (1), IVIG (1), and sirolimus (1), 1 underwent splenectomy
- Rituxan group: ADAMTS13 inhibitor [2.3 vs 1.8], total PLEX [21 vs. 9], inpatient stay [22 vs. 7]

- **TMA**

- IVIG (5), Imuran (2), cyclophosphamide (1), Cellcept (1), Tacrolimus (1)

# Summary



- **Severe ADAMTS13 deficiency in setting of thrombocytopenia and MAHA separates TTP from TMA**
- **Despite discontinuation of PLEX, mortality in TMA was lower (4%) than TTP (7%)**
- **If we had treated TMA with TTP PLEX regimen, some would have been considered to be good responders with normal ADAMTS13!**

# Conclusions



- **ADAMTS13 appears to have a diagnostic (but not prognostic) value in distinguishing TTP from TMA**
- **Patients with non severe deficiency should be managed without aggressive PLEX**
- **ADAMTS13 should be included as a triad for diagnosis of TTP along with MAHA and thrombocytopenia**
- **RCT would be helpful in this regard but....**

# Future Direction



- **Standardize ADAMTS13 testing, reduce TAT, and increase sensitivity (<1% activity? similar to hemophilia A)**
- **Triggering events that cause exacerbations, if any**
- **Any associations between TTP and diseases with immune dysregulation [SLE, HIV, other MCTDs]**
- **Proteins that modulate VWF/platelet/ADAMTS13/endothelium interaction**