The International Registry of Recurrent and Familial HUS/TTP: a tool for investigating rare diseases

Arrigo Schieppati
Thrombotic Thrombocytopenic Purpura
Hemolytic Uremic Syndrome

TTP and HUS are rare syndromes of microangiopathic hemolytic anemia and thrombocytopenia, which have in common thrombotic occlusion of the microvasculature of various organs.
Thrombotic Thrombocytopenic Purpura

Incidence: 4 cases per 1 million/year

More frequent among women (female/male ratio 3:2)

Most often acquired ("sporadic")

Relapses are frequent, one third of cases is recurrent

Familial TTP usually manifests in the postnatal period or during infancy, although in some cases the onset is later at 20-30 years

Patients with familial TTP typically exhibit a relapsing course
Deficiency of the von Willebrand Factor (VWF)-cleaving protease, *ADAMTS13*, has been reported in the majority of patients with TTP.

*ADAMTS13* deficiency may be either constitutive, due to mutations in the *ADAMTS13* gene, or acquired due to the presence of circulating anti-*ADAMTS13* autoantibodies.
vWF-Cleaving protease

Member of ADAMTS family (*A* Disintegrin-like *And* *M*etalloprotease, with *T*hrombo*S*pondin type 1 motif)

Named ADAMTS 13

1427 aa residues

Genomic DNA mapped to human chromosome 9q34

mRNA detected in liver

Gerritsen et al., *Blood*, 2001
Fujikawa et al., *Blood*, 2001
Soejima et al., *J Biochem*, 2001
Hemolytic Uremic Syndrome

Typical (Stx-associated)
Shiga-like toxin/verotoxin (Stx)-producing bacteria cause hemorrhagic colitis
Commonest form of AKI in children
Favourable outcome: < 10% of patients progress to ESRD

Atypical (Non-Stx-associated)
Rare: < 10% of all HUS cases
Familial or sporadic, any age.
Poor outcome: 50 to 60% of patients reach ESRD at the 1st episode
HUS OUTBREAK IN GERMANY
May 22 – July 26, 2011

4,321 persons infected with E. coli 0104:H4

- HUS 852
- deaths 50*

* 1 in Sweeden

Robert Koch Institut - Press release July 26, 2011
Germany Says Bean Sprouts Are Likely E. Coli Source
By ALAN COWELL
Atypical HUS

- **Sporadic**
  - Bacteria (*Streptococcus pneumoniae*)
  - Viruses (HIV)
  - Drugs (antineoplastic, antiplatelet, immunotherapeutic)
  - Post-transplant
  - Pregnancy-associated, Post-partum
  - Systemic diseases
  - Idiopathic

- **Familial** (less than 2% of cases)
  - autosomal dominant
  - autosomal recessive
Atypical HUS

Extensive research has established an association between aHUS and uncontrolled activation of the alternative pathway of the complement system.

Noris & Remuzzi *NEJM* 2009
Complement pathway

**Alternative pathway**

Gram+, gram-, bacteria, bacterial toxins, LPS

C3

C3a

C3b

C3bBb

C3 convertase

C3a

C3b

(C3b)_2 Bb

C5 convertase

C5

C5a

C5b

C5b-9 (MAC)

**Classical pathway**

Antigen-antibody complexes

C1

C4b

C4a

C4b-2a

C2

C2a

C4b3b.2a

C3 convertase

C5

C5a

C5b

C5b-9 (MAC)
• CFH ➔ Complement Factor H
• CFI ➔ Complement Factor I
• CFB ➔ Complement Factor B
• MCP ➔ Membrane-cofactor protein
Lancet 1978 Oct 21

Haemolytic-uraemic syndrome: deficiency of plasma factor(s) regulating prostacyclin activity?

G. Remuzzi et al.
Clinical Research Center for Rare Disease
1992
MARIO NEGRI INSTITUTE FOR PHARMACOLOGICAL RESEARCH
CLINICAL RESEARCH CENTER FOR RARE DISEASES ALDO E CELE DACCO'

International Registry of Recurrent and Familial HUS/TTP

REGISTRATION FORM
Through an International Network, we could collect the largest biological bank in the literature. We collected clinical data and biological samples from 900 cases of aHUS/TTP.
<table>
<thead>
<tr>
<th>Participating Centers</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>900</td>
</tr>
<tr>
<td>aHUS</td>
<td>696</td>
</tr>
<tr>
<td>TTP</td>
<td>285</td>
</tr>
<tr>
<td>AGE RANGE</td>
<td>1-80y</td>
</tr>
<tr>
<td>MALE/FEMALE</td>
<td>389/511</td>
</tr>
</tbody>
</table>
Flow-chart for biochemical-genetic analyses in patients with aHUS

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Serum complement (C3, C4, FH)</td>
<td>All patients with aHUS</td>
</tr>
<tr>
<td>Sequencing of <em>CFH</em> gene</td>
<td>All patients with aHUS</td>
</tr>
<tr>
<td>Sequencing of <em>CFI</em> gene</td>
<td>Pts with aHUS, without <em>CFH</em> mutations</td>
</tr>
<tr>
<td>Sequencing of <em>MCP</em> gene</td>
<td>Pts with aHUS, without <em>CFH/CFI</em> mutations</td>
</tr>
<tr>
<td>Sequencing of <em>C3</em> gene</td>
<td>Pts with aHUS, without <em>CFH/CFI/MCP</em> mutations</td>
</tr>
<tr>
<td>Sequencing of <em>THBD</em> gene</td>
<td>Pts with aHUS, without <em>CFH/CFI/MCP/C3</em> mutations</td>
</tr>
<tr>
<td>Sequencing of <em>CFB</em> gene</td>
<td>on a research basis only at present</td>
</tr>
<tr>
<td>Factor H auto-antibodies</td>
<td>on a research basis only at present</td>
</tr>
</tbody>
</table>
273 patients with aHUS

191 sporadic forms

42 familial forms

144 “idiopathic”

47 secondary
Fattore H 76 mutations

C3 12 mutations
Paris

CFI 23 mutations
Paris

Fattore B 5 mutations

MCP 28 mutations

THBD 6 mutations

Newcastle
Paris
Bergamo
Madrid
COMPLEMENT ABNORMALITIES IN 272 PATIENTS

Cumulation incidence (%)

- Factor H: 25%
- C3: 9%
- MCP: 6%
- Factor I: 5%
- Factor H ab: 4%
- Factor B: 2%
- Combined: 3%
- ?: 46%
- aHUS manifested during infancy in most patients
- The earliest onset was in subjects with CFH or THBD mutations
- A second pick was around 30 years of age, often in association with pregnancy

Noris et al CJASN 2010
TRIGGERING /UNDERLYING CONDITION

% of HUS patients

- Upper respiratory tract infection
- Diarrhea
- Pregnancy

Noris et al, CJASN 2010
OUTCOME OF THE FIRST EPISODE

Noris et al CJASN 2010

*P<0.05 vs MCP

Overall population
Children (60%)
Adults (40%)

% of events (ESRF or death)

0 10 20 30 40 50 60 70 80

no mut CFH CFI C3 THBD MCP

Noris et al CJASN 2010
LONG TERM OUTCOME OF aHUS PATIENTS

Patients free of events: Death or ESRD (%)

Follow up (years)

Noris et al., CJASN, 2010
SURVIVAL ACCORDING TO COMPLEMENT MUTATIONS

Patients alive (%)

C3 mutation

CFI

MCP

CFH

(p<0.01 vs others)

Noris et al., CJASN, 2010
Atypical compared to typical HUS is associated with an increased risk of recurrence after kidney transplantation.

Is the outcome of kidney graft for atypical HUS dependent on the genetic background of the disease?
78% of CFH mutation carriers had at least one graft failure. In 87% of them the cause of graft failure was HUS recurrence.
Of eight patients with CFI mutations, seven (88%) had recurrence and all lost their graft within one year.


Among patients with CFI mutations from the International Registry the incidence of HUS recurrence in the kidney graft is 80%.

Noris et al, *CJASN* 2010
Among patients with C3 mutations from the International Registry 4 out of 7 grafts were well functioning at >1 year post transplant

Noris et al, CJASN 2010

The kidney graft contributes to extrahepatic synthesis of C3
In 21 kidney transplant recipients 4-9% of circulating C3 plasma pool was of donor origin

Tang S et al, J Immunol 1999
No HUS recurrence in 10 out of 12 kidney grafts.

MCP is a membrane-bound protein highly expressed in the kidney. A dysfunction in MCP can be corrected by transplanting a normal kidney.

Noris and Remuzzi, *Am J Transplant* 2010
Conclusions

- The International Registry of Recurrent and Familial form of HUS/TTP proved to be an important tool to gather clinical information on this conditions.

- The results underline the need of genetic screening for complement abnormalities as part of clinical management of aHUS and for identification of patients who could safely benefit from kidney transplant.

Noris et al, CJASN 2010
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