Acquired Drivers of Disease
aHUS and autoantibodies: their role in disease and their impact on patient management

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Disclosure of Interests

- Alexion: consultancy; member of the Registry SAB
- Achillion: Consultancy
- Novartis: consultancy
Anti -Factor H antibodies : epidemiology

- First report in 2005\(^1\); Robust association with aHUS
- First cause of aHUS in children with aHUS onset between 5-11 years\(^2\)
- In Children and Adult onset
- Identified in 5 -14% in European cohorts but more than 50% in south Asia\(^3\)
- With FH-anti FH Immune Complexe in plasma

Determine triggers for production of anti FH Ab
Why this age specific occurrence

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Anti-Factor H antibodies : epitope mapping

More frequently IgG (IgG3); Polyclonal (cases of monoclonal)
Bind preferentially within the C-terminal domains of the proteins

Anti-Factor H antibodies: pathogenesis

Alternative pathway consumption in 30% of the cases
Induce FH deficiency with disruption of cell protection

Sheep Er lysis assay

Normal plasma

Plasma containing Ab anti-FH

Lysis

Determine whether functional assays identify patients with increased risk of relapse

1. Blanc et al. JASN, 2012; Blanc et al 2015;
Anti-Factor H antibodies: genetic background

- In association with CFHR1 deficiency in 85% (2 to 10% in healthy controls)
- Screening strategy: Multiplex ligation dependant amplification and western blot


CFHR1/CFHR3 or CFHR1/CFHR4 deletion
Link between CFHR1 deletion and haplotype FH 3 CAG
Anti -Factor H antibodies : genetic background

Study of genetic background for 13 patients with anti FH Ab from the UK cohort

- Rare variant (FH, FI, C3) no CFHR1
- Rare variant (CD46) with 2 copies of CFHR1
- No variant and 2 copies of CFHR1
- No variant no CFHR1

30% of rare variants in complement genes

Why patients with auto Ab lack CFHR1 protein?
What is the role of the associated rare variant?

Anti –Factor H antibodies: clinical features

• In Children and Adult onset
• Severe Illness with extrarenal manifestation (liver, pancreas, digital gangrene)
• Long-term evolution of the disease (death, renal sequel, cardiac insufficiency, non _auto immune diabetes)
• Risk of post transplantation recurrence is determined by the titre of anti FH Ab

Prodromes (n = 32)
- gastrointestinal symptoms
- infection
- other

84% (diarrhea: 53%)
(2 cases with Mallory-Weiss syndrome)
4 (1 varicella, 1 upper respiratory tract infection, 1 STEC, 1 norovirus)
2 urticaria and face edema

Clinical symptoms at onset (n = 32)
- hypertension
- hematuria
- oligo-anuria
- seizures
- pancreatitis
- hepatitis

68% 27% 23.5% 23.1% 50%

Anti –Factor H antibodies: diagnosis

Screening by ELISA (publication of the assay standardization, no commercial CQE)

Dose dependent binding to Factor H, results in UA /ml

One standard provided by Marie Agnes Dragon Durey (24 laboratories worldwide)

Usefull for monitoring disease activity

Screening at onset, at day 7, 14 and 28 after diagnosis, then monthly and 1/year

Monitoring for relapses and peri transplantation management with the anti FH titers


Lack of quality controls
Anti–Factor H antibodies: Treatment

- Plasma Exchanges and IS are recommended

1. Loirat et al. Pediatric Nephrol, 2015
Others acquired forms

- Anti FH Ab with/without MGUS (IgA isotype)

- Three reported cases of anti FI Ab without identified functional consequences

- Autoantibodies to CD59, CD55, CD46 or CD35 are not associated with Ahus

- Others: anti C3b