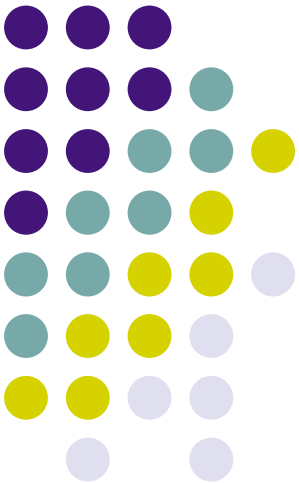

bjh guideline

Clinical Practice Guidelines for the management of atypical Haemolytic Uraemic Syndrome in the United Kingdom



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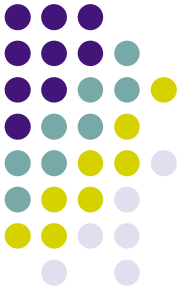
SUH

- Caracterizado por triada: Insuficiencia renal aguda + anemia hemolítica microangiopatíca + trombocitopenia
- D+ / D-
  - SUH ATIPICO
  - Desordenes del complemento
  - Pobre pronostico renal

Table I. Classification of thrombotic microangiopathies. Adapted by permission from Macmillan Publishers Ltd: Besbas *et al* (2006). Those conditions which might be included under the heading of aHUS are highlighted.

Advanced understanding of aetiology
Infection induced
Shiga and verocytotoxin (shiga-like toxin)-producing bacteria
Streptococcus pneumoniae
Disorders of complement regulation
Genetic disorders of complement regulation
Acquired disorders of complement regulation, for example anti-FH antibody
ADAMTS13 abnormalities
ADAMTS13 deficiency secondary to mutations
Autoantibodies against ADAMTS13
Defective cobalamine metabolism
Quinine induced
Aetiology not fully understood
HIV
Malignancy
Drugs
Pregnancy
Systemic lupus erythematosis and antiphospholipid antibody syndrome

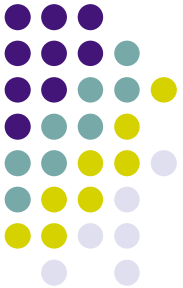
Infecciones



- Bacterias productoras de toxina Shiga y Shiga like
  - E. coli entero hemorrágica
  - SUH D+ → enfermedad aguda autolimitada con recuperación espontánea de la función renal

- Streptococco Pneumoniae
  - Productor de neuraminidasa

Complemento



- 30% mutaciones del gen que codifica la porción soluble del factor H (FH)
- 10% autoanticuerpos contra FH (mas frecuente en niños), asociado a deficiencia de la proteína relacionada al factor H
- 10% mutaciones del CD46 (MCP)
- 10% mutaciones del factor I (FI)
- Mutaciones activadoras del factor B y C3

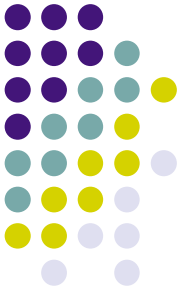
LAS MUTACIONES DE MÀS DE UNO DE ESTOS GENES AUMENTAN LAS POSIBILIDADES DE SUH

Deficiencia de ADAMTS13

- Congénito (niños)

- Adquirido → anticuerpos

Defectos del metabolismo de la cobalamina



- Defectos en el metabolismo intracelular de la cobalamina, predisponen a la microangiopatía trombotica

- Homocisteinuria + aciduria (metilmalònico)

- Habitualmente relacionado con mutación del factor H

aSUH

- Incidencia 2 casos / millón / año
- 5% de todos los SUH
- Mas frecuente en niños y adultos jóvenes

Evaluación Inicial

- C3 ⇩
- C4 ⇳
- Factor H
- Factor I
- Anticuerpos contra los componentes del complemento

Recommendation

In all patients presenting with clinical features compatible with a diagnosis of aHUS serum levels of C3, C4, factor H and factor I should be measured as the results guide prognosis and transplantation options. (strong, moderate).

FACS

Fluorescent-activated cell sorting (FACS) analysis

- Medición de la expresión de CD46 en los linfocitos de sangre periférica

Mala respuesta al tratamiento
Mal pronostico

Recommendation

In all patients presenting with clinical features compatible with a diagnosis of aHUS expression of CD46 on PBMCs should be assessed using FACS analysis in an appropriately accredited laboratory as the results guide prognosis and late transplantation options. (strong, moderate).

Estudios genéticos

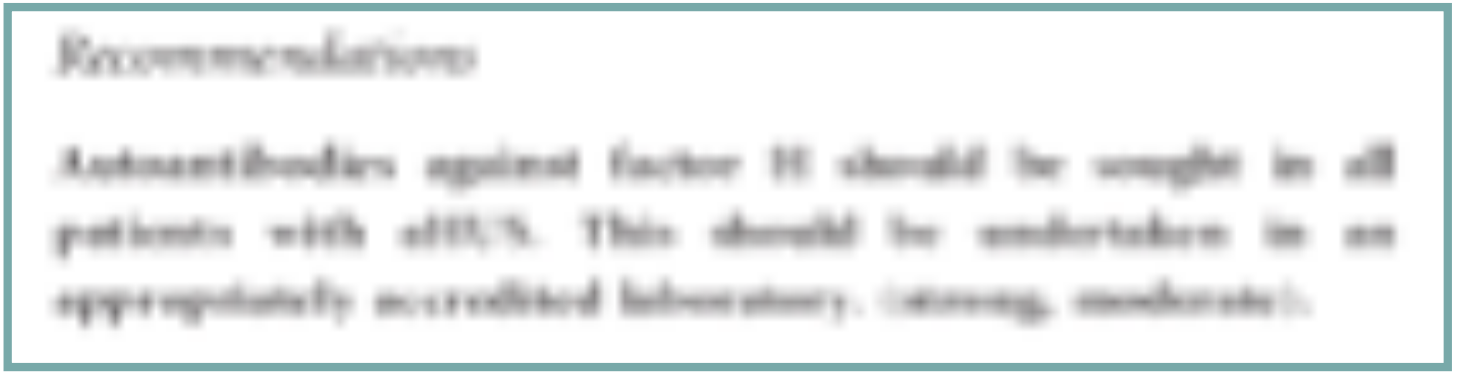
- Los niveles normales de FH, FI o MCP, no descartan la posibilidad de mutantes normalmente expresados pero funcionalmente deficientes

Recommendations

Mutation screening of *CFH*, *CD46*, *CFI*, *CFB* and *C3* should be undertaken in all patients with aHUS. This includes all historical cases that are being considered for transplantation. This should be undertaken in appropriately accredited molecular diagnostic laboratories and include appropriate techniques to detect copy number variation and hybrid genes. If mutations are found in other genes in the research setting then these should be incorporated into the molecular diagnostic portfolio. (strong, moderate).

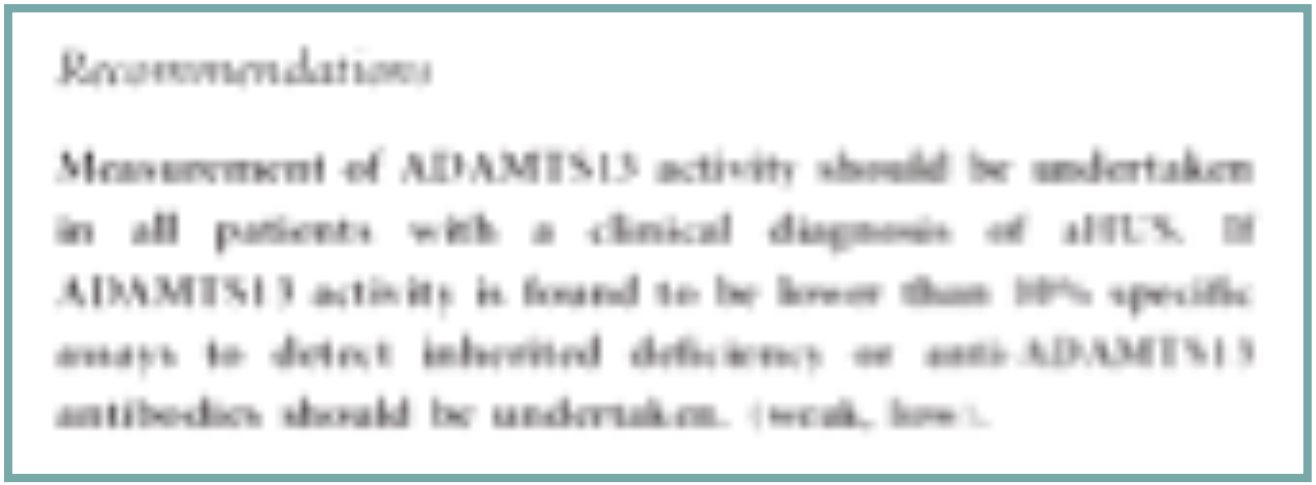
Screening de auto Ac

- Entre un 6 y un 10% de los pacientes con aSUH poseen autoAc que se unen a la porción C-terminal del factor H
- ELISA



Medición e Interpretación de ADAMTS 13

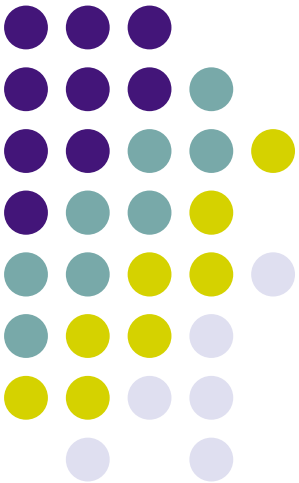
- PTT
  - Deficiencia constitucional
  - Anticuerpo inhibidor adquirido
- aSUH
  - Disminuyen los niveles (raramente <5%)



Recommendations

Measurement of ADAMTS13 activity should be undertaken in all patients with a clinical diagnosis of aHUS. If ADAMTS13 activity is found to be lower than 10% specific assays to detect inherited deficiency or anti-ADAMTS13 antibodies should be undertaken. (weak, low).

Manejo del aSUH



Plasmafèresis / Plasma

- Tratamiento de primera línea
- Plasmafèresis
  - Recambio de 1-2 volemias diarias inicialmente
  - Duración del tratamiento según la respuesta clínica
- Infusión de plasma
  - Diariamente al inicio, condicionada por HTA y manejo volumétrico

Recommendations

All patients presenting with aHUS should be offered a trial of plasma exchange and/or plasma infusions. (weak, low).

Pronostico

- 25% de mortalidad a la presentación
- 50% no recuperan función renal

Trasplante Renal

- Recurrencia 50% en el injerto, con incidencia variable según la anormalidad subyacente
- Mutación del FH o FI, pobre pronostico, 80% de perdida del injerto a los 2 años por enfermedad recurrente
- Pacientes con mutación de CD46 presentan buen outcome (la proteína es reemplazada con la del injerto)
- AutoAc contra FH, información es escasa pero con tendencia a una alta tasa de recurrencia

PMF y Rituximab podrian mejorar el outcome

Trasplante Renal

Recommendations

Renal transplantation alone is not recommended in patients known to have a *CFH* or *CFI* mutation. Patients carrying an CD46 mutation, but no additional mutation in factor *CFH*, *CFI*, *CFB* and *C3* or an anti-factor H autoantibody can be informed that the risk of recurrence post-transplantation is low. Patients known to have a *C3* or *CFB* mutation should be informed that current evidence suggests that there is a significant risk of disease recurrence post-transplantation. Patients known to have an anti-factor H autoantibody should be treated to minimise the antibody titre before proceeding to renal transplantation. Living related renal transplantation alone should be avoided in aHUS. (strong, moderate).

Trasplante Doble

- Los factores H e I son producidos en el hígado
- En pacientes con enfermedad renal estable y frecuentes recaídas, pese al tratamiento con plasma, se podría considerar trasplante hepático

Recommendations

In aHUS patients with a known mutation in either *CFH* or *CFI* consideration should be given either an isolated liver or a combined liver/kidney transplant as part of an internationally coordinated clinical trial. Within the UK an advisory panel should be established to consider all patients prior to listing. Within the UK, liver transplantation alone or in combination with a kidney transplant should only be undertaken in a limited number of centres with appropriate expertise. (weak, low).

Eculizumab

- Anticuerpo monoclonal humano de alta afinidad que se une y bloquea el clivaje de C5
- Su acción se desarrolla distal a las proteínas mutadas