INFLUENZA B-ASSOCIATED ATYPICAL HAEMOLYTIC UREMIC SYNDROME

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INTRODUCTION

Influenza A infections have been described to cause haemolytic uremic syndrome and to trigger atypical haemolytic uremic syndrome (aHUS) in individuals with an underlying genetic complement dysregulation. To date, Influenza B has only been reported to trigger aHUS in 2 patients. In 61% of aHUS cases, mutations are found in H, B and I factors, membrane cofactor protein (MCP), C3 and thrombomodulin. MCP (CD46) mutations account for 10-15% of cases.

CASE DESCRIPTION

PERSONAL, FAMILY AND CLINICAL HISTORY

- 13-year-old boy, transferred to a tertiary Intensive Care Paediatric Unit (ICPU) with anuria in the context of aHUS.
- Two pneumonia episodes at the age of 3. Irrelevant family history. Vaccinated according to National Vaccination Program. Missing flu-vaccination in the present year (though he was vaccinated in previous years).
- Flu-like syndrome (max. temperature 38.8ºC, cough, abdominal cramps and vomiting) in the previous 2 days. Reference to dark-colored urine and one episode of haematemesis at admission.
- Clinical presentation at admission: Icteric. MAP 129/84 mmHg. Few petechial lesions on the right shoulder, abdomen and trunk. No meningeal signs.

LABORATORY AND IMAGING STUDIES

- **Analysis** at admission (see graphic 1 for laboratorial evolution)*

  Hb 11,8→ 10,3 g/dL, rare schizocytes;
  Leucocytes 6300 → 4900/mm^3;
  Platelets 10.000 → 8.000
  Urea 83 → 89 mg/dL Creatinine 1,14 → 1,21 mg/dL (GFR 49 ml/min/1,73 m^2)
  ALT 52 UI/L Direct Bilirubin 2,3 mg/dL Total Bilirubin 5,2 mg/dL LDH 7961 Direct Coombs Test Negative
  Haptoglobin <0,08
  Blood gas and lactate: Normal
  Urine analysis: Proteins 3+ Hb 3+ Granular cylinders

- **Torax radiography:** Normal.
- **Abdominal and renovesical ultrasound:** "mildhepatomegaly, spleen dimensions in the upper limit of normality (120x51 mm) and increased renal ecogenicity"

DIAGNOSTIC HYPOTHESIS

HUS secondary to Influenza B infection?
versus
aHUS due to complement mutation, with Influenza B virus as a trigger?

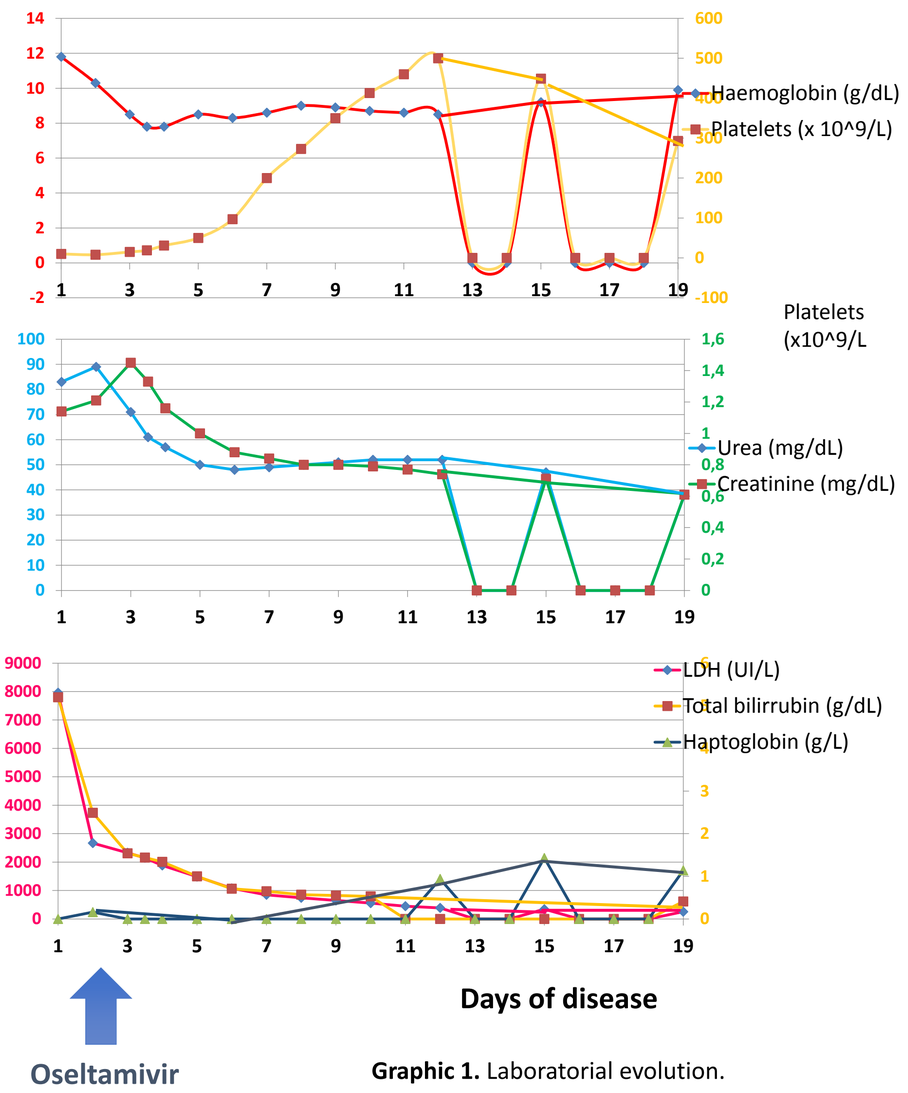
AETIOLOGIC INVESTIGATION

PCR for Influenza: **POSITIVE** for **Influenza B**. Negative for **Influenza A**.
Negative respiratory syncytial virus. Negative **HBs antigen**, **Hep C antibody**, **anti-HIV 1+2 antibodies**.
Negative **Strepto A antigen**.
Negative urinary ***S. pneumoniae*** antigen.
Negative urine PCR for **Leptospira**.
Negative **lupic** anticoagulant.
Decreased C' 3 levels (0,81 g/L) Normal **C' 4** levels (0,27 g/L).
Negative results for **anti-Beta2 GP1 IgG/IgM**, **anti-neutrophil-citoplasm-PR3** and **MPO** antibodies.
AH 50 112% of normal value (reference value >70%).
ADAMTS 13 activity**: 0,79** (values above 0,67 may be found in aSHU as well as other microangiopathic trombopathies).

MOLECULAR STUDY of complement including 11 genes* revealed a pathogenic **heterozygotic missense variant on CD46 (MCP) gene, c.554A>G, p.Asp185Gly, associated with aHUS**

*CFH, CD46 (MCP), CFI, C3, THBD, CFB, CFHR5, CFHR1, CFHR3, CFHR5, DGKE

LABORATORIAL EVOLUTION



Graphic 1. Laboratorial evolution.

CLINICAL EVOLUTION AND TREATMENT

- Patient stayed in ICPU for 3 days, with favourable clinical and analytical evolution.
- Transferred at day 4 to Nephrology Unit with progressive normalization of renal function. Normal blood pressure. Normal diuresis.
- 5 day treatment with **Oseltamivir** and **Cefotaxime**.

Treatment with ECULIZUMAB not performed

- **Good clinical and laboratorial evolution**
- **Detection of heterozygotic mutation in molecular study**

But... Close clinical and laboratorial follow-up!

To be started if another relapse!

CONCLUSIONS

- aHUS patients **should be screened** for **all known disease-associated genes**. Screening **should not be stopped** after finding a mutation, in order to avoid other genetic susceptibility factors influencing gene phenotype, particularly in patients with ***MCP* or *CFI* mutations**.
- The decision on whether treating or not with eculizumab should be made based on clinical and laboratorial evolution as well as molecular studies results.
- Influenza B is a trigger for aHUS and might be underreported as such. **Influenza vaccination** may protect patients at risk.

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