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 38.8°C, 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/mm³;
  Platelets 10.000 → 8.000
  Urea 83 → 89 mg/dL, Creatinine 1,14 → 1.21 mg/dL (GFR 49 ml/min/1.73 m²)
  ALT 52 U/L, Direct Bilirubin 2,3 mg/dL Total Bilirubin 5.2 mg/dL
  LDH 7961 Direct Coombs Test Negative
  Haptoglobin <0,08
  Blood 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


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-citoplasma-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, CFHRS, CFHR1, CFHR3, CFHRS, DGKE

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.