Varicella as a trigger of atypical haemolytic uraemic syndrome associated with complement dysfunction: two cases

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Abstract
We report two cases of children who presented with haemolytic uraemic syndrome following varicella infection. One of them had a membrane cofactor protein mutation, and the other had anti-factor H antibodies. These observations show that infectious agents such as varicella-zoster virus may be the trigger of haemolytic uraemic syndrome in patients with complement dysregulation.

Keywords: anti-factor H antibodies; haemolytic uraemic syndrome; MCP mutation; varicella

Introduction
Approximately 60% of atypical haemolytic uraemic syndromes (aHUS) have been shown to be related to complement dysregulation associated either with mutations in complement regulator factor H (CFH), factor I (CFI), membrane cofactor protein (MCP or CD46), factor B (CFB) or C3 [1–3] or with anti-CFH autoantibodies [4–6]. Although common infectious events such as upper respiratory tract infections or gastroenteritis appear to trigger HUS episodes in approximately two-thirds of aHUS patients [1,2], the occurrence of aHUS after specific bacterial or viral infections is exceptional. We report two cases of aHUS associated with complement dysfunction revealed after varicella infection.

Case reports
A 5-year-old boy [patient 1 (Figure 1)] presented with non-post-diarrhoeal HUS 17 days after varicella infection. Laboratory evaluation showed elevated serum creatinine concentration (270 µmol/L), anaemia (haemoglobin 6.5 g/dL), thrombocytopenia (platelets 19 G/L) and schistocytosis (17%). Search for Shigatoxin producing Escherichia coli (STEC) using PCR in the stool sample and serum antibodies against STEC O serotypes, and for methylmalonic aciduria, was negative. Anaemia and thrombocytopenia normalized within 1 week and glomerular filtration rate within 14 days, without dialysis requirement. One month after onset, plasma ADAMTS13 activity was 87% (normal values 50–150%), and C3, CFH and CFI levels were normal or elevated. Genetic investigation showed no mutations of CFH and CFI. MCP expression on the granulocyte surface was below the normal range and a heterozygous C30 F mutation in MCP exon 2 (c.191G>T) was demonstrated (Table 1).

After 5 years of follow-up, the boy has a normal glomerular filtration rate without hypertension or proteinuria. No recurrence of HUS has occurred.

A 4-year-old girl [patient 2 (Figure 1)] presented with non-post-diarrhoeal HUS 5 days after varicella infection. Laboratory evaluation showed elevated serum creatinine concentration (270 µmol/L), anaemia (haemoglobin 7.8 g/dL), thrombocytopenia (platelets 35 G/L) and schistocytosis. Search for STEC using PCR in the stool sample and serum antibodies against STEC O serotypes, and for methylmalonic aciduria, was negative. A kidney biopsy showed diffuse glomerular thrombotic microangiopathy. After spontaneous improvement of HUS, two relapses occurred within 6 weeks after onset. A plasma exchange (PE) programme was started at Month 2 after onset, with fresh frozen plasma for restitution (60 mL/kg/session, five sessions/week × 2 weeks), which was rapidly beneficial. Two relapses occurred at Months 3 and 5, ∼14 days after PE discontinuation. PE exchange was subsequently maintained until normalization of glomerular filtration rate at Month 9 (i.e. a total of 39 PE). The child had only mild hypertension during the next 12 years. Ten years after onset, C3, C4, CFB, CFH and CFI levels were normal, but anti-CFH antibodies and a deletion of CFH-related genes CFHR1-CFHR3 were demonstrated. No mutations of CFH, CFI or MCP were found (Table 1). Anti-CFH antibodies remain positive 13 years after onset, with normal C3 and CFH levels.
Table 1. Complement components assessment

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Normal values</th>
</tr>
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<tbody>
<tr>
<td>Delay after onset</td>
<td>1 month</td>
<td>10 years</td>
<td></td>
</tr>
<tr>
<td>CH50 (%)</td>
<td>152</td>
<td>NA</td>
<td>70–130</td>
</tr>
<tr>
<td>C3 (mg/L)</td>
<td>1340</td>
<td>668</td>
<td>660–1250</td>
</tr>
<tr>
<td>C4 (mg/L)</td>
<td>226</td>
<td>208</td>
<td>93–380</td>
</tr>
<tr>
<td>CFB (mg/L)</td>
<td>280</td>
<td>99</td>
<td>90–320</td>
</tr>
<tr>
<td>CFH (%)</td>
<td>154</td>
<td>90</td>
<td>70–130</td>
</tr>
<tr>
<td>CFI (%)</td>
<td>167</td>
<td>89</td>
<td>70–130</td>
</tr>
<tr>
<td>MCP expression (MFI)</td>
<td>380</td>
<td>981</td>
<td>600–1400</td>
</tr>
<tr>
<td>Anti-CFH antibodies</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(252 AU)</td>
<td></td>
</tr>
<tr>
<td>CFH gene</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>MCP gene</td>
<td>C30F (p.Cys64Phe; c. 191 G&gt;T; TGT&gt;TTT)</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>CFI gene</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>CFHR1-CFHR3 deletion</td>
<td></td>
</tr>
</tbody>
</table>

MFI = mean fluorescence intensity; AU = arbitrary units.

Fig. 1. Evolution of HUS in the 2 patients. — serum creatinine (µmol/L); ••••• platelets (10³ G/L); —— haemoglobin (g/L); ||||| plasma exchanges.

Discussion

Varicella (due to varicella-zoster virus (VZV) of the Herpesviridae family) is a predominantly childhood disease characterized by a vesicular exanthema frequently accompanied by fever and malaise. Human VZV disseminates to the viscera during viraemia and then multiplies in reticuloendothelial tissues. Varicella usually results in mild to moderate illness but serious complications (meningoencephalitis, meningitis, vasculitis affecting small or large vessels, pneumonia and haemorrhages) can arise [7]. However, there has been only one previous report of HUS following varicella infection [8].

Both our patients presented with typical varicella infection with fever and vesicular rash, followed within 5–17 days by HUS. They were investigated for complement anomaly because they were STEC negative, and varicella is not considered as a possible direct aetiology of HUS. In addition, patient 2 had several relapses of HUS during the first 6 months after onset. Patient 1 was shown to have decreased expression of MCP and a heterozygous C30F mutation in exon 2 of MCP. This mutation has not been reported in other aHUS patients [9], and its functional consequences are unknown. However, the change of one cystein that plays a major role in the structure of this transmembrane protein may modify its expression. It is well known that a
triggering event is necessary for HUS to occur in patients with complement genetic abnormalities. Two children with MCP mutations and STEC-associated HUS have been reported (patient 20[2], [10]), one of them with a fulminant fatal outcome [10].

Patient 2 was shown to have anti-CFH autoantibodies 10 years after onset. VZV is known to induce autoimmunity, such as anti-protein S and anti-phospholipids antibodies [11]. However, varicella has not been reported as the initial event in patients with aHUS associated with anti-CFH antibodies. The sequence of events between varicella and aHUS remains hypothetical. Indeed, varicella may trigger the process of autoimmunity in patients with a genetic susceptibility linked to CFHR1-R3 deletion. Another hypothesis could be based on cross-reactivity between VZV antigen and CFH protein. In such a case, the absence of CFHR1-R3 could lead to a preferential binding of antibodies to CFH, leading to its inactivation.

These observations raise the question of the prevention of varicella in children known to have aHUS, especially if associated with complement dysfunction. To our knowledge, varicella has not been reported as the triggering event of HUS episodes in the cohorts of aHUS that mostly include children [1,2]. However, one child with a C3 mutation and severe varicella that triggered a relapse of HUS has been reported (A. Lahoeche, Lille, personal communication, with permission). Finally, we recommend that parents of children with aHUS, and no clinical history of varicella nor anti-varicella antibodies, should receive the following information: avoid contact with children with overt varicella, give oral acyclovir if the child develops varicella, to diminish and shorten the viral load and eventually prevent HUS relapse. We also recommend IV acyclovir in patients with a first episode of HUS triggered by varicella. There is no consensus for vaccination in children with aHUS, due to limited information on the frequency of HUS episodes after immunization. Most probably, the benefit of vaccinations (prevention of the viral or bacterial infections which may trigger relapses) outweighs their risk (a triggering effect of relapses from vaccination), as in other immunological diseases. Our option is to perform obligatory and anti-influenza vaccinations in children who have aHUS, whatever their genetic background, as well as vaccination against *Streptococcus pneumoniae* and *Neisseria meningitidis* in those with very low C3 (homozygous CFH deficiency, gain of function CFB or C3 mutations). However, there is no experience of anti-varicella vaccination in children with aHUS so that no guideline can be drawn.

In conclusion, these two cases outline that varicella may trigger aHUS associated with complement dysregulation, either constitutional (MCP mutation) or acquired (anti-CFH autoantibodies in patients with CFHR1-CFHR3 deletion). aHUS triggered by varicella should lead to extensive screening of the complement system in order to identify susceptibility factors.

**Conflict of interest statement.** None declared.

**References**


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