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ORIGINAL ARTICLE

Occurrence of atypical HUS associated with influenza B

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Abstract Hemolytic uremic syndrome (HUS) is a disease characterized by thrombotic microangiopathy with a triad of non-immune hemolytic anemia, thrombocytopenia, and renal impairment. Approximately 10% of cases of HUS are classified as atypical (aHUS). While today many genetically forms of aHUS pathology are known, only about 50% of carriers precipitate the disease. The reason remains unclear, and triggering events like intercurrent infections have been postulated. In rare cases, influenza A is the known trigger of aHUS; however, no cases of influenza B have been reported.

Conclusion: We describe for the first time that influenza B strain as a trigger for aHUS in children with primary hereditary forms. We also showed in our three cases that immunization appears to be safe; however, this needs to be confirmed in a larger cohort.

Communicated by Mario Bianchetti

Electronic supplementary material The online version of this article (doi:10.1007/s00431-017-2856-5) contains supplementary material, which is available to authorized users.

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What is Known:
• *Known triggers of aHUS are infectious specimen.*
• *Influenza A-associated aHUS cases are rarely published.*

What is New:
• *aHUS can be triggered by influenza B virus infection.*
• *Influenza vaccination of patients with aHUS appears safe.*

Keywords Atypical hemolytic uremic syndrome · Hemolytic uremic syndrome · Influenza B · Vaccination

Abbreviations

aHUS	Atypical hemolytic uremic syndrome
CFH	Complement factor H
eGFR	Estimated glomerular filtration rate
EHEC	Enterohemorragische *Escherichia coli*
HUS	Hemolytic uremic syndrome
MCP	Membrane cofactor protein
TTP	Thrombotic thrombocytopenic purpura

Introduction

Hemolytic uremic syndrome (HUS) is characterized by thrombotic microangiopathy with a triad of non-immune

hemolytic anemia, thrombocytopenia, and renal impairment [1, 2]. Ninety percent of the cases are caused by verotoxin-producing *Escherichia coli* (EHEC) and are coined as typical or D+ HUS because of the history of hemorrhagic colitis [1, 2]. HUS is classified as atypical (aHUS) in approximately 5–10% of cases [1–3]. aHUS has an incidence of two per million population per year [4] and is a serious life-threatening disease with progression to end-stage renal disease in 50 to 80% of the cases (depending on the underlying defect) [1, 2, 5]. Many triggers are known to induce aHUS including infections with *Streptococcus pneumoniae*, Epstein-Barr virus, varicella, and human immunodeficiency virus [1, 2]. In rare cases, influenza A was reported as a trigger of aHUS [3]. However, no cases of aHUS triggered by influenza B have been described so far.

During the winter of 2012–2013, three patients presented at our department with an aHUS most likely triggered by influenza B virus infection. In all three patients, an extensive etiological work-up was performed. Different investigations could exclude the presence of the EHEC bacteria or *Shigella dysenteriae* type 1 neither on stool, blood, nor urine samples. Other viruses such as Epstein-Barr virus, cytomegalovirus, and hepatitis A, B, or C were not detected. Thrombotic thrombocytopenic purpura (TTP) was ruled out based on normal ADAMTS13 (Von Willebrand factor-cleaving protease) activity. There was no evidence of a secondary aHUS due to autoimmune disease. Screening was negative for anti-nuclear factor antibodies, anti-nuclear cardiolipine antibody, anticardiolipine, and lupus anticoagulant. No clinical evidence of lupus erythematosus was detected. Normal homocysteine and the absence of methylmalonic acidemia ruled out a cobalamin deficiency. On personal history, no medication use could be identified as a trigger of aHUS. No defect was found in the complement regulatory proteins (normal serum total complement, C3, C4, complement B, H, and I). Genetic testing revealed in all patients later on an underlying genetic complement dysregulation.

Case reports

Patient one

A previously healthy 10-year-old boy was transferred to our hospital with a suspicion of aHUS. He presented with a 3-day history of flu-like symptoms. His parents consulted because of progressive illness, jaundice, drowsiness, and macroscopic hematuria.

Physical examination showed an alert child with a blood pressure (BP) of 123/79 mmHg (P95, 121/81 mmHg). Petechiae on the lower limbs, jaundice, and mild peripheral edema were present. Blood results are shown in Table 1. He was admitted for supportive treatment (fluid, furosemide

infusion, and platelet and packed cell transfusion). During the hospitalization, the kidney function declined with a maximum serum creatinine of 2.06 mg/dl (estimated glomerular filtration rate (eGFR) calculated with the Schwartz formula of 29 ml/min/1.73m^2) and oliguria, without electrolyte disturbances. Recovery was observed after 1 week with conservative treatment and normalization of serum creatinine 1 month later.

Family history revealed that the maternal grandmother and her sister were known with end-stage renal disease (ESRD) due to aHUS with low C3, but undefined genetic cause. Genetic testing in our patient revealed a heterozygote mutation in the C3 gene (c.481C>T (p.Arg161Trp) in exon 4) [4, 6, 7].

Patient two

A 15-year-old boy known with aHUS due to a primary hereditary complement disorder presented with the third recurrence of aHUS after flu-like symptoms since 2 days and no history of diarrhea. He has a heterozygote mutation in the clusterin gene (c.1298A>C (p.Thr433Asn) in exon 7) and a heterozygote mutation in the membrane cofactor protein gene (MCP, c.811-816delGACAGT(p.Asp271-Ser272del) in exon 6) [8, 9] as described previously [5].

At presentation, he had a BP of 135/90 mmHg (P95, 133/84 mmHg) and orbital and peripheral edema of the lower limbs due to oliguria and acute kidney insufficiency with a serum creatinine of 4.1 mg/dl (eGFR of 18 ml/min/1.73m^2). Initial laboratory findings are shown in Table 1. He was treated with plasma exchanges (six times in total) with improvement of diuresis and renal function. There was no need of dialysis or antiviral medication. Normalization of serum creatinine was seen 2 months later and remained stable during follow-up.

Patient three

The patient was a 9-year-old boy known with a previous episode of aHUS after a *Salmonella typhimurium* infection, with spontaneously recovery. He presented with a recurrence of aHUS after an episode of epistaxis, macroscopic hematuria, and flu-like symptoms since 2 days. On physical examination, he was euvolemic with a normal BP, petechiae on the lower limbs, and jaundice. Laboratory findings are shown in Table 1.

Genetic testing revealed a heterozygote mutation in the MCP gene (c.565T>G (p.Tyr189Asp) [6, 10]) and a heterozygote mutation in the CFB gene (c.26T>A(p.Leu9His), in exon 1) [11]. Plasma exchanges were started with improvement of the renal function and were stopped after six sessions. There was no need of dialysis or antiviral medication. Normalization of serum creatinine was seen 1 month later and remained stable during follow-up.

Table 1 Patients' blood, urine, and stool results at admission

1	Blood results	Patient 1	Patient 2	Patient 3	Ref value
	Hemoglobin (g/dl)	11.3	13	10.4	11.5–15.5
	Schistocytosis (/1000 RBC)	12–17	30–40	12–17	<5
	Platelet count ($\times 10^3/\mu l$)	25	20	22	150–450
	Creatinine level (mg/dl)	1.53	4.1	1.01	0.33–0.64
	Urea nitrogen level (mg/dl)	77	136	105	≤48
	Haptoglobin (g/L)	0.35	0.19	0.13	0.3–2.0
	LDH (U/l)	2920	5218	2700	135–250
	Total/direct bilirubine (mg/dl)	1.46/<0.18	3.8/1.1	1.73/0.27	≤1.0/ ≤0.5
	AST (U/l)	189	211	107	≤32
	ALT (U/l)	33	68	14	≤31
	Albumin (g/l)	35.5	35.1	39	35–52
	Total complement (%)	122	98	>145	70–140
	C3d (%)	8.4	10.1	7.3	≤2.4
	C4 (g/l)	0.26	0.14	0.29	0.16–0.34
2	Urine result				
	RBC (/μl)	52	106	Massive hematuria	0–5
	Protein/creat ratio (gr/gr creat)	12.58	4.08	4.76	<0.2
3	Nasopharyngeal swab				
	Influenza B	Positive	Positive	Positive	

The evolution of the hematological testing during hospitalization in all three patients are shown in supplementary figure 1

Because of flu-like symptoms, a nasopharyngeal swab was performed in all three patients and was positive for influenza B using the rapid antigen detection test. We suggested that the most probable diagnosis was an aHUS triggered by influenza B. All three patients (within the same flu season 2012–2013) were infected with the same B strain, from the B/Yamagata lineage as determined by sequencing of the hemagglutinin gene.

Discussion

We report for the first time three patients that presented with aHUS most probably triggered by influenza B virus infection during the same flu season before that eculizumab was available (2012–2013).

Etiologically, aHUS is a heterogeneous group with primary underlying genetic causes found in ~50% of the patients. These genetic defects are involved in the regulation of the alternative complement pathway on vascular endothelial cells. They include defects of complement factor H (CFH), factor I, factor B, thrombomodulin (CD141), C3, MCP (CD46), and autoantibodies against factor H with or without CFH-related protein 1 and 3 deficiency [1–3, 12, 13]. Also, Von Willebrand factor-cleaving protease deficiency or defective cobalamin metabolism is known to cause aHUS [1–3, 13]. Furthermore, aHUS can be secondary to systemic diseases characterized by microvascular injury (such as systemic lupus erythematosus) [1–3, 13] and can be triggered by medication (like calcineurin inhibitors, cytotoxic, chemotherapy agents, and quinine) or infectious diseases (like *S. pneumoniae*, Epstein-Barr virus, varicella, and human immunodeficiency virus) [1–3, 13–17]. In rare cases, influenza A viruses have been reported to trigger aHUS [3].

There are three types of influenza viruses (A, B, and C) of which A and B are known to cause illnesses in humans [18]. Most influenza infections are self-limited, but infants or patients with underlying medical conditions are at increased risk for complications attributable to influenza [19]. Various pulmonary, neurological, cardiac, and muscular complications of influenza virus infection have been reported [3]. Renal complications of influenza virus infections are uncommon but can lead to deterioration in patient's condition, such as acute kidney injury in critically ill patients, rhabdomyolysis, acute glomerulonephritis, disseminated intravascular coagulation, Goodpasture's syndrome, and acute tubulointerstitial nephritis [3, 20]. Also, influenza A has been described to trigger aHUS [3].

aHUS associated with influenza virus is extremely rare. We can divide the reports of aHUS triggered by influenza A into two major groups (Table 2): seasonal influenza A caused by epigenetic drift and pandemic H1N1 influenza A caused by epigenetic shift [3].

Only six patients have been reported so far with aHUS associated with seasonal influenza A [3, 21–25] where in two patients, the serotype of influenza A is defined as H3N2 (Table 2) [21, 22]. In two post-renal

Table 2 Overview of the described patients with aHUS triggered by influenza A (literature) and B virus (van Hoeve et al.)

Type			Publication y	Age	Sex	Underlying cause and treatment	Ref
Infl	A	Seasonal Infl A	Serotype				
	H3N2		2001	3y	F	Not known. Need for hemodialysis.	[21]
	H3N2		2000	35y	M	Postrenal transplant. Spontaneous recovery without dose reduction of cyclosporine.	[22]
	HxNx		1971	20y	F	Postrenal transplant. Need for transplantectomy.	[23]
	HxNx		1984				
	HxNx		1973	14y	F	Not known. Need for dialysis.	[24]
				14y	M	Not known. Dead due to massive hemoptysis.	[25]
	Pandemic H1N1	Subtype					
		Associated with S. pneumoniae	2010	3y	F	Positive cryptic Thomsen Treatment with hemo	[19]
		Associated with a genetic complement dysregulation	2011	15y	F	CD46 gene mutation (?). 5th episode of aHUS. Treatment with plasma exchange.	[27]
			2011	15y	M	Postrenal transplant due to aHUS. C3 heterozygous gene mutation. Treatment with plasma exchange and eculizumab	[28]
			2011	27y	M	Low C3. Treatment with plasma exchange.	[29]
			2011	17y	M	Mutation in membrane cofactor protein. Treatment with dialysis and plasma exchange.	[30]
		Without any known underlying disorders	2011	11y	M	Not known. Treatment with plasma exchange.	[31]
			2011	7y	M	Not known. Treatment with plasma exchange and peritoneal dialysis.	[32]
			2011	5y	F	Not known. Treatment with hemodialysis.	[33]
Infl	B	Associated with a genetic complement dysregulation	20- 13		Co-	mplement dysregulation suspected (genetic testing pending). Positive family history of HUS.	10y [a]
M			15y		M	Mutation in the clusterine gen and membrane cofactor protein gen	
9y	M	Complement dysregulation suspected (genetic testing pending). 2nd recurrence of aHUS.					

Overview of all patients in the literature with aHUS triggered by influenza virus A and our patient series triggered by influenza B. The population of aHUS triggered by influenza A can be divided into two major groups: seasonal influenza A and pandemic H1N1 influenza A. The H1N1 group can on this turn be divided into three groups (S. pneumoniae-associated HUS following H1N1 infection; HUS triggered by H1N1 in patients with genetic complement dysregulation; and HUS associated with H1N1 without any known underlying disorders)

Inf A influenza A, *Inf B* influenza B, *F* female, *M* male, *y* year

[a] van Hoeve et al.

transplant patients, the use of immunosuppressants may also have triggered aHUS [22, 23, 26].

Influenza A virus has eight separate gene segments [18]. Reassortment of genes between two strains of influenza (humans, avian, swine, etc.) can create a pandemic strain of influenza A to which humans have no protective immunity [18]. In 2009, due to epigenetic shift, influenza A (pH1N1) reappeared [18] and in a short period, more cases of aHUS were described in the literature, namely eight patients worldwide (Table 2) [19, 27–33]. It is not clear whether the virulence of the influenza A virus is important in causing or triggering aHUS [18]. In the literature, the pandemic group can be divided further into three groups (Table 2) [3]: (1) S. pneumoniae-associated HUS following H1N1 infection;

(2) HUS triggered by H1N1 in patients with genetic complement dysregulation (four persons [27–30]); and (3) HUS associated with H1N1 without any known underlying disorder (three persons [31–33]). Although in the latter group, a thorough search in each patient to rule out a genetic complement dysregulation has not been done [3].

S. pneumoniae-associated HUS following influenza infection was only described in one patient [19]. S. pneumoniae is known to trigger HUS [3, 15, 18, 19]. Therefore, co-infection of S. pneumoniae should be sought in patients with aHUS following influenza infection [15, 18]. Influenza virus can precipitate the infection of the pneumococcus by inducing epithelial damage that predispose invasion of the pneumococcus, by exposure or upregulation of existing receptors and by

altering the immune response by diminishing the ability of the host to clear pneumococcus or due to activation of the inflammatory cascade [3].

Although the mechanisms of influenza A virus-associated HUS have not been elucidated, two hypotheses have been postulated. One hypothesis suggests an altered immune response with activation of mononuclear cell that produces tumor necrosis factor alpha [3, 21, 22]. The second hypothesis suspects unmasking the cryptic Thomsen-Friedenreich antigen on the red blood cells, platelets, and glomerular epithelia caused by viral neuraminidase of influenza A that cleaves sialic acid residues from various glycoproteins [3, 31, 32, 34]. This latter hypothesis has also been postulated in *S. pneumoniae*-associated HUS [31, 35]. Since this is the first case report on aHUS caused by influenza B strains, we assume that similar mechanisms are involved, but specific studies should be done to elucidate the pathophysiology.

In our series, the three patients presented with an aHUS triggered by influenza B had all an underlying genetic complement dysregulation. The three children received further follow-up and with the upcoming influenza season, the question was raised whether it would be safe or even advisable to vaccinate these patients with aHUS triggered by influenza.

In Belgium, the Superior Health Council recommends seasonal influenza vaccination for high-risk populations [36]. In Europe/Belgium, only inactivated influenza vaccines were available at the time, namely influenza vaccines consist of split virus particles (split virion) or specific purified hemagglutinin (H) and neuraminidase (N) (subunit). For the 2013–2014 Northern hemisphere influenza season, WHO recommended the following strains to be included in the seasonal influenza vaccine: an A/California/7/2009 (H1N1) pdm09-like virus; an A (H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011; and a B/Massachusetts/2/2012-like virus [37].

The next year, we decided to vaccinate our patients because of the lack of literature [38], and because vaccination is the only available mean to prevent influenza infection and therefore possible relapse. Also, the likelihood of influenza infection causing a recurrence of aHUS was perceived to be far greater than the possibility of the inactivated trivalent vaccine. Our three patients were vaccinated prior to the 2013–2014, 2014–2015, and 2015–2016 influenza season. We followed them very carefully and they did not relapse. From our experience, even though it is based on a small cohort of three cases, we would like to suggest that influenza vaccination can be presumed safe in this population. Whether the vaccination protects them for a recurrence is still open for discussion, since the infecting B strain in 2014–2015 was the same strain used in the 2013–2014 and the 2014–2015 influenza vaccine.

Conclusion

Influenza viruses are uncommon triggers of aHUS. Influenza A viruses have been recognized as a trigger for aHUS in the past. We describe that the influenza B strain is also capable of triggering aHUS in children with a genetic predisposition. We also showed that immunization of these children with an inactivated trivalent vaccine appears to be safe.

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