Severe *Bordetella Pertussis* Infection Associated with Hemolytic Uremic Syndrome

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Pertussis, caused by the bacterium *Bordetella pertussis*, remains a common infection even in the current vaccination era. It was previously categorized as an exclusively childhood disease; however, in recent years, a massive number of juveniles and adults have been infected by the disease. As a result, pertussis seems to constitute a major recent public health hazard when compared to its past occurrence.

The classical symptom of pertussis is a whooping paroxysmal cough most frequently observed in unvaccinated infants, who are also at the highest risk for pulmonary complications [1]. Among the hematologic manifestations, leukocytosis, lymphocytosis, and related pulmonary leukostasis have been identified as the most important findings in both pathogenesis and prognosis [1].

Hemolytic uremic syndrome is typically caused by an intestinal infection with verotoxin-producing *Escherichia coli*, leading to endothelial injury and renal microangiopathy (verotoxin-related or typical HUS). However, current evidence suggests that atypical HUS may also occur as a consequence of infection with non-enteric pathogens, including *B. pertussis* [2].

We describe an infant with severe pertussis who developed HUS during the paroxysmal stage of the disease, without evidence of VTEC infection.

HUS = hemolytic uremic syndrome

PATIENT DESCRIPTION

A 2 month old infant was admitted to the Department of Pediatrics with a paroxysmal cough and cyanosis of 2 days duration. He was born to healthy non-consanguineous parents at 31 weeks gestation. Delivery was by cesarean section because of breech presentation and premature rupture of the membranes. The postnatal course in the neonatal intensive care unit was uneventful. He was asymptomatic until 2 days before admission.

On physical examination, the infant weighed 3.275 g, body temperature was 38.4°C, heart rate 157 beats/min and respiratory rate 50 breaths/min. He was pale, tachypneic, and dyspneic with grunting. Intercostal and subcostal retractions were present. Paroxysmal cough leading to cyanosis was observed with oxygen saturation of 80% in room air. The lungs were clear, and there was no wheezing or rales. The rest of the physical examination was unremarkable. Oxygen supplementation was administered.

Chest X-ray film showed general over-aeration with subsegmental atelectasis in the right upper and left lower lobe and bilateral perihilar infiltrates. Laboratory investigation revealed a leukocyte count of 33,000 cells/ml with 55% lymphocytes. The remaining blood parameters were within normal range, including electrolytes, and liver and renal function tests. Following a complete sepsis workup, ampicillin and gentamicin were administered pending culture results. Azithromycin and methylprednisolone were subsequently added, but his clinical condition failed to improve. On day 5, the infant continued to have severe paroxysms and was extremely excitable. Repeated complete blood count revealed hemoglobin 11.4 g/dl, thrombocytosis 1,194,000/ml, and leukemoid reaction with leukocyte count 108,000 cells/ml, 34% neutrophils and 55% lymphocytes. There were no signs of leukemia on peripheral blood smear or bone marrow aspirate study.

VTEC = verotoxin-producing *Escherichia coli*

Nasal wash samples were negative for respiratory syncytial virus and adenovirus antigens. Serum samples were negative for antibodies against *Chlamydia pneumoniae* and *Chlamydia psittaci*. Polymerase chain reaction assay was positive for *B. pertussis*. A retrospective detailed history revealed that two other infants hospitalized in the neonatal intensive care unit during the patient's postnatal stay had acquired pertussis.

Ten days after admission the infant's clinical condition worsened. Severe respiratory distress, persistent hypoxemia, and frequent prolonged events of paroxysmal cough with intermittent cyanosis were documented. He was transferred to the pediatric intensive care unit for respiratory support and mechanical ventilation. Chest X-ray films revealed diffuse lung opacities compatible with acute respiratory distress syndrome. One day later, anemia (8.8 g/dl) and throm-

bocytopenia (50,000/ml) developed. Blood smear revealed fragmented erythrocytes. Oliguria and acute renal failure (creatinine 0.75 mg/dl, urea 72 mg/dl) were followed by hypertension (150/100 mmHg). Renal sonography demonstrated kidneys of normal size with increased echogenicity; echo-Doppler study of the renal vessels showed a normal pattern of arterial and venous blood flow. The working diagnosis was atypical HUS. Blood and urine cultures were sterile. Stool cultures were negative for *E. coli* 0157:H7. Complement (C3, C4, CH50) and factor H were within normal range.

Peritoneal dialysis was initiated, followed by continuous plasmapheresis. Hypertension was controlled with nifedipine and propranolol. After 10 days, progressive recovery of the renal function was observed and dialysis was discontinued. The patient was weaned from mechanical ventilation after 2 weeks.

After a total of 10 weeks hospitalization the infant was discharged home. Tests showed recovery from the respiratory insult and normalization of renal function (serum creatinine 0.35 mg/dl, urea 10 mg/dl) and hematologic indices (hemoglobin 11.5 g/dl, platelets 457,000/ml). At the monthly follow-up visits until the child was 1 year old, blood pressure, renal function and complete blood count were within the normal range. Mild chronic lung disease persisted.

COMMENT

Atypical HUS in a heterogeneous group of patients is associated with non-enteric infections (*Streptococcus pneumoniae*, human immunodeficiency virus), pregnancy, treatment with diverse drugs (calcineurin inhibitors, antineoplastic and antiplatelet agents), malignancies, collagen vascular diseases (systemic lupus erythematosus), prior transplantation, and childbirth [2]. It may be familial or sporadic. The differentiation of atypical from classical HUS is important for both treatment and outcome. Patients with atypical HUS are particularly prone to recurrence, often triggered by other infections. Atypical HUS also has a less favorable prognosis than HUS due to verotoxin [2], with reported mortality rates of up to 25% in the acute phase, a relapsing course in 50%, and end-stage renal disease in 60% [2].

According to recent studies, about half the cases of atypical HUS (familial and sporadic) are associated with mutations in genes encoding for complement regulators: factor H, factor I, and membrane cofactor protein (CD46); factor H plays the central role [2]. A low level or abnormal function of these inhibitory proteins results in uncontrolled activation of the alternative complement pathway, consumption of C3, and reduction of C3 serum levels. Additionally, autoantibodies for factor H have been described in patients with sporadic atypical HUS in the absence of genetic mutations [3]. Functional analysis revealed that autoantibodies interfered with complement regulatory decay [3].

The mechanism whereby factor H deficiency or dysfunction causes HUS remains unclear. The factor H abnormality probably predisposes patients to HUS but is insufficient to cause the infection by itself, and a second hit is needed. Researchers have suggested that avascular endothelial injury with subsequent subendothelial space damage, which in normal circumstances would spontaneously resolve, leads to complement activation that propagates excessively in the absence of factor H inhibition [3]. Indeed, the predominant pathological abnormality in atypical HUS is located in the renal arterioles and interlobular arteries. Widespread endothelial swelling with retraction leads to exposure of the basement membrane. As a result, the vessel lumens are occluded by red cells and platelet fibrin thrombi [2].

A possible association of atypical HUS with pertussis was first proposed by Berner et al. [4] reporting on a newborn in whom HUS developed several weeks after onset of severe whooping cough due to *B. pertussis* infection, with a fatal outcome. Factor H with abnormal mobility was found in the patient's serum. The authors concluded that in genetically predisposed patients, *B. pertussis* infection might trigger HUS. More recently, Chaturvedi and colleagues [5] described an infant who acquired HUS during the paroxysmal stage of severe pertussis, with no evidence of VTEC infection or factor H abnormalities. They suggested that *B. pertussis* may cause HUS even in children lacking predisposing factors.

The pathogenesis of *B. pertussis* infection is mediated by several virulence factors, including filamentous hemagglutinin, pertussis toxin, and adenylate cyclase toxin. Pertussis toxin, uniquely produced by *B. pertussis*, has long been known to cause systemic symptoms associated with pertussis disease, such as lymphocytosis, insulinemia/hypoglycemia, and histamine sensitivity [1]. However, vascular or renal effects have not been reported. Moreover, adenylate cyclase toxin is a secreted toxin targeting host phagocytic cells by binding complement receptor 3 (CR3; D11b/CD18), forming membrane pores and raising intracellular cAMP levels [1]. Further investigation of potential interactions between pertussis toxins and the alternative complement pathway are warranted as they may hypothetically explain the association of the pathogen with HUS.

In the present case, the clinical picture, epidemiology (two other cases of pertussis infection in children hospitalized in the neonatal intensive care unit at the same time as the patient), and positive polymerase chain reaction assay confirmed the diagnosis of *B. pertussis* infection. The clinical picture, similar to previous reports [4,5], was characterized by severe respiratory symptoms and an extreme

hematologic anomaly (leukemoid reaction of 108,000 cells/ml white blood cells and thrombocytosis of 1,194,000/ml), which may have served as predisposing factors for the unusual complication of pertussis. In our case, levels of complement C3, C4, CH50, and factor H were within normal range. Dysfunction of factor H, or other alternative complement pathway regulators, could have served as a predisposing factor for the HUS.

In conclusion, pertussis infection should be considered a plausible trigger of (atypical) HUS in cases where *E. coli* infection is not involved. The cascade of events remains unclear, but inflammatory cells, released toxins, and abnormal function of inflammatory pathways are probably involved in the development of microangiopathy and HUS. Further studies of the causative role of factor H abnormalities are warranted.

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References

1. Carbonetti NH. Immunomodulation in the pathogenesis of *Bordetella pertussis* infection and disease. *Curr Opin Pharmacol* 2007; 7: 272-8.
2. Jokiranta T, Zipel P, Fremeaux-Bacchi V, Taylor CM, Goodship TJ, Noris M. Where next with atypical hemolytic uremic syndrome? *Mol Immunol* 2007; 44: 3889-900.
3. Caprioli J, Noris M, Brioschi S, et al. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. *Blood* 2006; 108: 1267-79.
4. Berner R, Krause MF, Gordjani N, et al. Hemolytic uremic syndrome due to an altered factor H triggered by neonatal pertussis. *Pediatr Nephrol* 2002; 17: 190-2.
5. Chaturvedi S, Licht C, Langlois V. Hemolytic uremic syndrome caused by *Bordetella pertussis* infection. *Pediatr Nephrol* 2010; 25: 1361-4.

Capsule

Disease-promoting and -protective genomic loci on mouse chromosomes 3 and 19 control the incidence and severity of autoimmune arthritis

Proteoglycan (PG)-induced arthritis (PGIA) is a murine model of rheumatoid arthritis. Arthritis-prone BALB/c mice are 100% susceptible, whereas the major histocompatibility complex-matched DBA/2 strain is completely resistant to PGIA. To reduce the size of the disease-suppressive loci for sequencing and to find causative genes of arthritis, Glant et al. created a set of BALB/c.DBA/2-congenic/subcongenic strains carrying DBA/2 genomic intervals overlapping the entire *Pgia26* locus on chromosome 3 (chr3) and *Pgia23/Pgia12* loci on chr19 in the arthritis-susceptible BALB/c background. Upon immunization of these sub-congenic strains and their wild-type (BALB/c) littermates, we identified a major *Pgia26a* sub-locus on chr3 that suppressed disease onset, incidence and severity via controlling the complex trait of T cell responses. The region was reduced to 3 Mbp (11.8 Mbp with flanking regions) in size and contained gene(s) influencing the production of a number of pro-inflammatory cytokines. Additionally, two independent loci (*Pgia26b* and *Pgia26c*) suppressed the clinical scores of arthritis. The *Pgia23* locus (~3 Mbp in size) on chr19 reduced arthritis susceptibility and onset, and the *Pgia12* locus (6 Mbp) associated with low arthritis severity. Thus, we have reached the critical sizes of arthritis-associated genomic loci on mouse chr3 and chr19, which are ready for high throughput sequencing of genomic DNA.

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Eitan Israeli

Take a chance and you may lose. Take not a chance and you have lost already

Soren Kierkegaard (1813-1855), Danish philosopher and theologian, and critic of idealist intellectuals and philosophers of his time and of the state and practice of Christianity. He is widely considered to be the first existentialist philosopher

Give me a museum and I'll fill it

Pablo Picasso (1881-1973), Spanish painter, sculptor, printmaker, ceramicist and stage designer who spent most of his adult life in France. He is widely known for co-founding the Cubist movement. His revolutionary artistic accomplishments brought him universal renown and immense fortune, making him one of the best-known figures in 20th century art

I am free of all prejudices. I hate everyone equally

W.C. Fields (1880-1946), American comedian, actor, juggler and writer, known for his comic persona as a misanthropic and hard-drinking egotist