A newborn with pertussis accompanying nephrotic syndrome

Münevver Kaynak-Türkmen[1], Fulya Cengiz-Erdem[1], Ferah Sönmez[2], İlknur Girişgen[2], Murat Telli[3], Afig Berdeli[4]

Divisions of [1]Neonatology and [2]Pediatric Nephrology, Department of Pediatrics, and [3]Department of Microbiology, Adnan Menderes University Faculty of Medicine, Aydın, [4]Department of Medical Genetics, Ege University Faculty of Medicine, İzmir, Turkey.

E-mail: igirisgen78@hotmail.com

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Pertussis or whooping cough is a vaccine-preventable disease that still remains a serious infection in neonates and young infants. The disease is particularly severe in infants less than three months old, who are often infected by their parents. Congenital nephrotic syndrome is a rare entity presenting within the first three months. It encompasses a heterogeneous group of entities with genetic, infectious and idiopathic etiologies. In this report we describe a newborn infant who presented with congenital nephrotic syndrome secondary to Bordetella pertussis infection.

Key words: congenital, nephrotic syndrome, infection, pertussis, infant.

Whooping cough (pertussis), caused by the gram-negative bacterial pathogen *Bordetella pertussis*, is a highly contagious acute respiratory illness that can be prevented by vaccination[1-3].

Despite high vaccination coverage, over the last 15 years there has been a worldwide resurgence of *Bordetella pertussis* infection[4]. Adults are a reservoir for the transmission of infections to very young infants, in whom pertussis may be severe and life threatening. Neonatal cases are particularly challenging, with a risk of death up to 3%[5-9].

The most common cause of death from pertussis in young infants is pneumonia, which may be complicated by apnea, seizures and encephalopathy.

The onset of nephrotic syndrome within the first three months of life is classified as congenital[10,11]. Rarely do infants with congenital nephrotic syndrome (CNS) have secondary reversible disorders. Secondary CNS is often caused by immune-mediated injury to the glomerular basement membrane. Historically, congenital syphilis has been associated with nephropathy; however, various reports have also implicated toxoplasmosis[12], rubella[13], cytomegalovirus[14], HIV[15] and hepatitis B[16]. CNS has been reported in infantile systemic lupus erythematosus. Diphtheria, pertussis and tetanus are also causes of CNS[17]. Here, we describe a newborn male with CNS secondary to pertussis.

Case Report

A 23-day-old male infant was admitted to our clinic because of respiratory distress, breastfeeding difficulties, coughing and vomiting after coughing. He was delivered by cesarean section at another hospital to a 32-year-old mother (gravida 2 para 2) at 40 weeks of gestation. His birth weight was 3000 g. The pregnancy had been uneventful, and the maternal screens were all negative. The infant's mother had complained of a mild paroxysmal cough two weeks before and after delivery. The patient was referred to our clinic by another healthcare center because of leukocytosis and an elevated CRP level.

The infant's blood pressure was 96/49 mmHg, pulse 136/min, respiration rate 50/min and body temperature 36.2 °C. His weight was in the 50th-75th percentile; his height and head circumference were in the 90th percentile. Physical examination revealed mild to moderate respiratory distress; there were rales at the

upper zone of the right lung. Intermittent whooping cough attacks were observed. Laboratory evaluation showed a white blood cell count of 19500/μL, hemoglobin 11g/dl, hematocrit 33%, platelets 612000/mm^3 and C-reactive protein 120 mg/dI. His biochemical parameters were normal. Chest X-ray indicated bilateral pneumonic infiltrations. The infant was treated with ampicillin and cefotaxime because of leukocytosis and elevated acute phase reactants, and clarithromycin because of the provisional diagnosis of atypical pneumonia based on the whooping cough attacks. *Bordetella pertussis* PCR samples were taken from both the infant and the mother.

On the laboratory evaluation at the fifth day he was noted to have 9 g/dl hemoglobin, 27% hematocrit, 68000/mm^3 leukocytes and 592000/mm^3 platelets. A peripheral blood smear showed 48% PMNL, 35% lymphocytes, 5% monocytes, 5% band, 2% eosinophil and 5% myelocytes. The specimen was considered indicative of leukemoid reaction. Nasopharyngeal wash fluid was positive for *Bordetella pertussis* for both mother and infant. Specimens for *Bordetella pertussis* testing were collected with nasopharyngeal swabs. The High Pure PCR Template Preparation Kit (Roche Diagnostic Indianapolis, IN, USA) was used for bacterial DNA extraction from specimens. The presence of *Bordetella pertussis* was detected in specimens by polymerase chain reaction (PCR) using the Seeplex PneumoBacter ACE detection kit (Seegene, Inc, Korea). PCR was performed according to the recommendations of the manufacturer. The BP485 gene region was targeted for detection of *Bordetella pertussis*.

The patient was considered as showing a leukemoid reaction following *Bordetella pertussis* infection. He gained significant weight, and swelling of the eyelids and extremities was present. His biochemical tests were repeated and showed sodium: 127 mEq/L, total protein: 4.6 g/dl (N: 4.6-7.4), albumin: 2.4 g/dl (N: 2.5-3.4). Urine dipstick showed a specific gravity of 1.010 and protein 1+; urine microscopy was unremarkable and urine culture was sterile. The urinary protein/creatinine ratio was 2.7 (N<0.7). Repeated laboratory investigations showed triglycerides: 138 mg/dl (N: 38-105), LDL: 65 mg/dl (N: 25-65), total cholesterol: 119 mg/dl (N: 44-120). On the basis of these findings, he was diagnosed as congenital nephrotic syndrome. Infection was considered as a secondary cause. The following tests were used for differential diagnosis and found negative: TORCH panel, EBV IgM, hepatitis serology, ANA and anti-dsDNA (for neonatal lupus). Genetic analysis revealed no mutations in the *NPHS1* and *NPHS2* genes.

The patient was diagnosed as nephrotic syndrome secondary to *Bordetella pertussis* infection. He developed hypertension (110/70 mmHg) that was treated with enalapril. He was also noted to have significantly decreased urine output, which was treated with furosemide. He was given RBC transfusion because his hemoglobin value was 7 g/dl. Ultrasound examination of the kidneys and renal vessels was normal. By the 25th day of admission he was free of edema and proteinuria. At discharge, his laboratory findings and biochemical parameters were normal: urine protein was negative, total protein was 5 g/dl, and albumin was 3.1 g/dl. He was discharged with enalapril on the 35th day.

Discussion

Whooping cough is a highly contagious, potentially life-threatening respiratory tract illness caused by the gram-negative pleomorphic bacillus known as *Bordetella pertussis*[1-3]. Despite high vaccination coverage, over the last fifteen years there has been a worldwide resurgence of *Bordetella pertussis* infection[4]. In the first three months of life it is frequently severe and often fatal. In our case, the mother was the reservoir of pertussis, with symptoms and positive PCR. Neonatal infection carries a particularly serious risk of death, up to 3%[5-9]. The initial finding is frequently apnea; although the affected babies cough, their cough is so faint that it often goes unrecognized. Seizures due to hypoxia resulting from apnea are common. Severe pulmonary hypertension is therefore frequently the cause of death[18-19]. In our case, ECHO was normal. In young infants, the severity of disease and risk of death correlates directly with the white blood cell count and in particular the number of lymphocytes[5,9,20-22].

Leukemoid reaction is a usual presentation of pertussis. It is a moderate, advanced or sometimes extreme degree of leukocytosis, which is similar to that occurring in leukemia but is due to some other cause. Conventionally,

leukocytosis exceeding 50000 WBC/mm^3 with a significant increase in early neutrophil precursors is referred to as leukemoid reaction. There is a mix of early mature neutrophil precursors, in contrast to the immature forms typically seen in leukemia. The absence of blasts in the peripheral smear helped us to exclude leukemia. The hyperleukocytosis seen in our case was probably due to leukemoid reaction secondary to pertussis, which is a usual presentation. Further, the WBC counts promptly normalized in response to appropriate antibiotics.

Other risk factors for fatal disease in young infants are premature birth and the presence of pneumonia[22]. PCR, culture and serology are the main methods of laboratory diagnosis[1,23]. However, in recent years, PCR has been more popular and has significantly contributed to the diagnosis of pertussis[24]. In our case, the use of PCR made rapid diagnosis of pertussis possible.

Maternal vaccination offers the possibility of protecting the infant from birth until immunity is achieved by active vaccination. Neonatal vaccination, on the other hand, will leave the infant susceptible to pertussis for a period of weeks to months. The optimal timing of maternal vaccination is 30-32 weeks. Transplacental pertussis antibody concentrations in newborn babies were found to decline with a half-life of around 6 weeks, and by the age of 2-6 months most infants had no detectable antibodies to *Bordetella pertussis*[25].

The onset of nephrotic syndrome within the first three months of the life is classified as congenital. CNS is a rare entity characterized by massive proteinuria, severe hypoalbuminemia and edema, presenting within first three months of life[10,11].

Primary NS includes the autosomal recessive hereditary syndromes and entails genetic changes in glomerular structure. *NPHS1* and *NPHS2* mutations cause abnormality of the slit diaphragm[10,11]. Rarely do infants with congenital nephrotic syndrome have secondary reversible disorders. Secondary CNS is often caused by immune-mediated injury to the glomerular basement membrane. Historically, congenital syphilis has been associated with nephropathy; however, various reports have also implicated toxoplasmosis[12], rubella[13], cytomegalovirus[14], HIV[15] and hepatitis B[16]. CNS has been reported in infantile systemic lupus erythematosus. Diphtheria, pertussis and tetanus are also causes of CNS[17].

In the present case, the patient had proteinuria, hypoalbuminemia, edema and hyperlipidemia. These findings indicated congenital nephrotic syndrome. We considered the case as secondary nephrotic syndrome given the lack of birth edema, the uneventful antenatal history and the occurrence of proteinuria following infection. Mutation analysis was also requested to rule out primary nephrotic syndrome. The test came back negative.

Treatment of secondary NS means treatment of the underlying cause. The regression of proteinuria after treatment of pertussis in our patient supports this approach. CNS often requires a long hospitalization and albumin transfusion. Recurrent infections, growth retardation and electrolyte disorders are common[26]. Our patient showed significant improvements in his percentile status during follow-up.

In conclusion, pertussis is a disease rarely encountered in the etiology of secondary NS. Due to both pertussis and the complications of NS, such cases are at risk for morbidity and mortality. The patient described here is the first documented case of congenital nephrotic syndrome secondary to pertussis in Turkey.

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