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Detection Of Respiratory Syncytial Virus (Rsv) At Birth In A Newborn With Respiratory Distress

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ABSTRACT: Respiratory syncytial virus (RSV) is the most common respiratory pathogen in infants and young children. From the nasopharyngeal or conjunctival mucosa of infected individuals, RSV spreads to the lower respiratory tract causing acute bronchiolitis and pneumonia after an incubation period of 4 to 6 days. In addition to its well-documented tropism for the airway epithelium, it has been shown previously that RSV can also spread hematogenously and efficiently infect extrapulmonarytissues of human hosts. Furthermore, it has been shown in animal models that RSV can spread transplacentally from the respiratory tract of a pregnant mother to the lungs of the fetus. This report describes a documented case of neonatal RSV infection strongly suggestive of prenatal transmission of this infection in humans from an infected mother to her offspring.

KEYWORDS: Asthma & Early Wheeze; Critical Care; Developmental Biology; Infections: Pneumonia; TB;Viral; Neonatal Pulmonary Medicine

1. INTRODUCTION

Respiratory syncytial virus (RSV), an enveloped, non-segmented, negative-sense RNA virus belonging to the Paramyxoviridae family, is the most common respiratory pathogen in infants and young children [1], resulting in approximately 24 hospitalizations per 1,000 infants and an estimated 66,000–199,000 annual deaths worldwide in children younger than 5 years, with 99% of these deaths occurring in developing countries [2]. After entering the host through the nasopharyngeal or conjunctival mucosa, RSV spreads to the lower respiratorytract where it can cause acute disease characterized by edemaand necrosis of the respiratorymucosaleading to airflow obstruction [3]. The incubation period ranges from 2 to 8 days but usually is 4 to 6 days [1].In addition to its well-documented tropism for the human airway epithelium, RSV is able tospreadhematogenously from the primary site of infection to remote extra-pulmonary tissues [4,5], particularly the bone marrow stromal cells that may provide the virus with an immunologically privileged sanctuary and allow its persistence in latent state [6]. Expanding on these findings, RSV has been shown recently to spread across the rodent placenta from the respiratory tract of an infected dam to the lungs of the fetus[7]. However, so far vertical transmission of this virus has been demonstrated in animal models, but never in humans.

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Herein, we describe a case of RSV infection documented at birth in the peripheral blood of a human newborn with onset of severe respiratory distress immediately after delivery from a mother with serological and clinical evidence of RSV infection during pregnancy.

2. CASE REPORT

Patient was a baby boy born in September 2016 at 35 weeks gestational age via emergency caesarean section performed for reduced fetal movements. Maternal serologic screening for TORCH infections [Toxoplasmosis, Syphilis, Varicella-Zoster Virus (VZV), Parvovirus B19, Rubella, Cytomegalovirus (CMV), and Herpes Simplex Virus (HSV)], Hepatitis C Virus (HCV), Hepatitis B Surface Antigen (HBsAg), and Human Immunodeficiency Virus (HIV), as well as screening test for Group B Streptococcus were all negative. The newborn was second born of non-consanguineous parents and family history was unremarkable. Birth weight was 3,550 g (>95%ile) and Apgar score was 8 at both 1-minute and 5-minute time points. Clinical examination was normal for gestational age, but postnatal cardio-respiratory adaptation appeared suboptimal because of nasal flaring and severe chest retractions. Therefore, positive pressure ventilation was started with FiO2 of 0.21. Physical examination revealed a newborn with grunting respiration, rales in both lungs, tachycardia (185/min), tachypnea (60/min) and oxygen saturation of 92% on room air (Silverman-Andersen score = 4). Umbilical arterial blood analysis revealed a pH of 7.18, partial O2 pressure of 32 mm Hg, partial CO2 pressure of 68 mm Hg, and a base deficit of −11.8 mmol/l. Chest radiography at birth showed diffuse fine and granular opacities, and mild perihilar linear opacities bilaterally suggestive of respiratory distress syndrome. Broadspectrum antibiotic coverage and minimal enteral feeding via gavage were started, and the patient was transferred to the Neonatal Intensive Care Unit for non-invasive ventilation via nasal continuous positive airway pressure (nCPAP) at 5 cm H2O. In light of the clinical and laboratory findings, an umbilical venous catheter was placed. Complete blood counts and serum chemistry tests yielded normal values, and all blood and urine cultures were negative.

After one week of nCPAP, the patient still required ventilatory support. Therefore, new chest radiography was obtained at 10 days of life, which revealed the presence of an area of consolidation in the parahilarregion of the right lung. At the same time, cultural andserological microbiological tests were undertaken, which detected weakly positive anti-RSV IgM (1/20) and markedly positive anti-RSV IgA (1/60) and anti-RSV IgG (1/160) titers.

Furthermore, RSV RNA was amplified from the newborn's peripheral blood obtained on the first day of life using standard operating procedures to safeguard the sterility of the sample and analyzed with a high-sensitivity quantitative real-time RT-PCR assay. The analytical sensitivity threshold of this test is 250 copies/ml,and thus results are interpreted as positive if the RSV copy number detected in the sample is above threshold. This test also ruled out the presence of more than 40 other common viral and bacterial respiratory pathogens, including: Influenza (A, B), Parainfluenza virus (1, 2, 3, 4), Rhinovirus (A, B, C), Enterovirus (A, B, C, D), Adenovirus (A, B, C, D, E, F, G),Mycoplasmapneumoniae, Bordetella pertussis, HSV, VZV, CMV, Epstein-Barr Virus(EBV), and Human Herpes Virus 6 (HHV6).

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In light of clinical and microbiological findings in the newborn, maternal serologic tests were also performed and showed elevated anti-RSV IgM (1/40), IgA (1/20) and IgG (1/60) titers. Reassessment of maternal prenatal and familial history, revealed that the newborn'smother and other family members had complained of cough during the second trimester of gestation. All other diagnostic tests performed on the newborn during the course of hospitalization, including brain and renal ultrasound, electrocardiography, echocardiography, and auditory/visual function screening, showed normal findings. At 17 days of life, the patient's respiratory status improved and in parallel serologic RSV test became negative (IgM: negative; IgA: negative; IgG 1/80). Patient was discharged home in good health on day 22 of life.

3. DISCUSSION

RSV is the major respiratory pathogen in young children, causing substantial morbidity and mortality worldwide [2].The clinical course of the first infection varies from mild upperrespiratory tract symptoms to severe lower respiratory tract disease (bronchiolitis or pneumonia) leading to hospitalization in 2–3% of cases 10. Reinfections are common, but usually less severe or asymptomatic[10]. The mode of transmission of this infection has always been thought to be horizontal (interpersonal) and through direct contact with infected secretions. However, recent experimental evidence has suggested that also vertical transplacental transmission may occur.

Due to ethical constrains, vertical transmission of RSV infection so far has been demonstrated only inexperimental animal models .[8] The present report is relevant in that it describes a neonatal case of human RSV infection consistent with vertical transmission from a previously infected mother to her unborn son. In this newborn with symptoms consistent with viral pneumonia since birth, microbiological tests revealed high serum titers of antiRSVIgM, IgA, and IgG, as well as presence of RSV RNA in blood samples obtained with sterile procedure on the first day of life. Serologic tests for RSV were also positive in the mother and correlated with a history of respiratory symptoms during gestation in several members of the immediate family, suggesting an infectious etiology.

Previously, only the possibility of antenatal RSV sensitization has been investigated [11],showing that RSV-specific neutralizing antibodies are not only efficiently transferred via theplacenta to the newborn[12], but also protect the newborn against RSV infection during thefirst months of life [13]. Importantly, prenatal RSV exposure modified theexpression of genes encoding growth factors critical for development of the peripheralnervous system, particularly affecting the cholinergic innervation of the airways and leadingto bronchial hyperreactivity[14].The case described in this report may be the first clinical description of vertical transmissionof RSV in a newborn, reproducing the experimental conditions used in Piedimonte's rodentmodel [8]. Indeed, the newborn's mother reported cough during the pregnancy, which wasassociated with serological evidence of RSV infection. Her newborn showed evidence offetal distress in utero and was born in respiratory distress with onset of the respiratorysymptoms immediately after birth in September, i.e., before the peak of RSV epidemicgenerally occurring between October–November and May–June in Southern Italy.

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As thepre- and peri-natal history of our patient was unremarkable for all possible etiologies of fetaland neonatal respiratory distress, vertical RSV infection appears to be the only plausibleexplanation of the clinical manifestations.It should be noted that the incubation period for RSV ranges from 2 to 8 days, after whichthe clinical infection starts with signs and symptoms of mucosal inflammation and irritationof the upper respiratory tract (congestion, rhinorrhea, sneezing). Over the next several days,the clinical status evolves with involvement of the lower respiratory tract manifested bycough and increased work of breathing with use of accessory respiratory muscles toovercome the increased resistance of obstructed airways. In the case described, the lowerrespiratory tract symptoms were already present at birth, which is not consistent withinfection after birth but rather suggest that the infection had occurred before birth.

The viraletiology was confirmed in the newborn both by serology and PCR, and corresponded topositive serology for the same virus in the mother. Thus, all historical, clinical anddiagnostic information converge in suggesting vertical transmission of RSV from the motherto the offspring.When considering direct transmission of viral pathogens from mother to offspring, it isessential to understand that the pathological consequences may be significant despitepreexisting maternal seroimmunity, as demonstrated by the relevant congenital morbidityand mortality observed after secondary infections with other viruses, such as CMV andpestivirus. Furthermore, in our previous studies performed in rodent models, all RSVinfected dams developed measurable anti-RSV antibody titers, and yet they were often ableto transfer the infection to their fetuses[8], and these models have been highly predictive ofhuman pathology for several other vertically transmitted viruses, such as CMV, arenaviruses,or parvoviruses . Finally, our finding of vertical transmission in animals provides the onlyplausible explanation for the repeated isolation of blood-borne RSV in the first days of lifeof unexposed human newborns.

As in all case reports, several limitations caution against generalization of our findings. In particular, RSV serology is not standardized and generally not used to make definitive diagnosis of acute infection. Specifically, as IgG cross the placenta, neonatal anti-RSV IgGwere likely of maternal origin, and IgM can produce false positives (interference with high titerIgG and other similar viruses). However, several studies have previously demonstrated that the IgA detected in neonatal blood is primarily of fetal origin [11]. In normal development, fetal IgA is either undetectable or rises very slowly during gestation and fetallevels at term remain approximately 1,000 times lower than concentrations in the maternal circulation [15]. Secretory IgA is then transferred to the newborn by breastfeeding [17], but our patient did not receive breast milk in the NICU. Thus, a positive IgGtiter indicates that the fetus has “inherited” maternal antibodies, but positive IgA – especially at the high titersfound in our patient (1:60) – together with positive IgM at birth suggest strongly that the fetus had been vertically infected. At any rate, these serology results were confirmed in our patient by the detection of clinically relevant amounts of RSV RNA. In addition, to excludeco-infections and/or super-infections, we performed extensive serological tests as well asdetection of other RNA viruses (e.g., adenovirus, rhinovirus, coronavirus, virus influenza,virus parainfluenza, metapneumovirus, and enterovirus) that resulted all negative.

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Another potential limitation is that we do not have a nasopharyngeal swab or bronchoalveolar lavage for RSV detection in the respiratory tract of this newborn. Nevertheless, given the extremely low chance of horizontal transmission, it is reasonable to think that the infection had started prenatally. If so, the studies by Piedimonte et al. [8]indicated that pups exposed to RSV infection in utero develop strong bronchial hyperreactivity to either electrical nerve stimulation or methacholine challenge after postnatal reinfection with the same virus. Therefore, newbornswith early respiratory distress associated with evidence of RSV infection warrant closer follow-up for the possible recurrence of wheezing.

More importantly, the possibility that RSV is transmitted vertically from mother to fetus has the potential of changing our strategies for the prevention and therapy of this highly prevalent infection and its chronic sequelae. The most important implication is that the passive prophylaxis with humanized monoclonal antibodies currently offered only to infants at high risk for severe infection should probably be anticipated to expecting mothers in order to prevent prenatal infections. Such protection could be provided in a perhaps more effective, safer, and less expensive way by actively immunizing pregnant women with a suitable vaccine, which could be provided to large segments of the population even in third world countries where RSV is still an important cause of infant mortality.

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