ACUTE RESPIRATORY DISTRESS SYNDROME IN A CHILD WITH HUMAN PARVOVIRUS B19 INFECTION

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Abstract: A 6-year-old girl developed shock and multiple organ dysfunction including acute respiratory distress syndrome in association with parvovirus B19 infection. The diagnosis was based on positive antibodies and the detection of parvovirus 19 DNA in serum, bronchial secretions and skin biopsy. It seems likely, but it was not proved, that the parvovirus infection caused acute respiratory distress syndrome.

Key Words: human parvovirus B19, multiple organ disfunction syndrome, acute respiratory distress syndrome, nitric oxide

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Human parvovirus B19 (PB19) usually causes erythema infectiosum, a common childhood benign condition with a typical slapped-face rash.[1,2] Infection can be asymptomatic[1] or uncommonly give rise to a variety of clinical manifestations: chronic anemia; arthritis; transient aplastic crisis; thrombocytopenia; neutropenia; myocarditis; hepatitis; meningitis; encephalitis; atypical rash; hydrops fetalis; and congenital anemia.[1,2] PB19 can cause a mild respiratory tract illness with no rash, but there are also reports of acute obstructive respiratory disease and severe pneumonia.[3,4]

CASE REPORT

A 6-year-old girl presented with fever, sore throat, abdominal pain and myalgia. She had a history of asthma controlled with montelukast. Two weeks previously she had a slapped-face rash, and on the second day of disease she developed a maculopapular exanthema over the thighs. Hemoglobin, platelet and white blood cell (WBC) count were normal but C-reactive protein was 30.5 mg/dL. The urine analysis revealed >50 WBC per high power field. After blood and urine bacterial cultures, therapy was started with ceftriaxone for probable urinary tract infection.

On the third day, the patient was admitted to her local emergency department. The exanthema was petechial and spread over the abdomen, arms and legs, reaching the soles and palms, resembling rickettsiosis. She developed labored respiration, poor perfusion, hypotension, lowered consciousness and conjunctival hemorrhage. Her respiratory condition deteriorated with bronchospasm and increasing needs for oxygen. She was transferred to a university hospital and admitted to the Pediatric Intensive Care Unit, requiring tracheal intubation and mechanical ventilation. Chest radiograph and PaO_2:FiO_2 ratio were consistent with acute respiratory distress syndrome (ARDS).

Initial treatment included aggressive pressure-controlled ventilation, salbutamol, sedatives, analgesics, inotropic support and cefotaxime, clarithromycin and ciprofloxacin. On admission, hemoglobin had dropped to 8.4 g/dL requiring 2 red blood cell transfusions, and platelets reached a minimum value of 86×10^9/L. A coagulation study revealed a prolonged activated partial thromboplastin time and prothrombin time: 47.1 and 16.8 seconds, respectively. Liver function tests were abnormal; maximum total bilirubin and transaminases were 4.5 and 2.1 times normal, respectively. Total WBC counts remained normal with lymphocytopenia during first 5 days. C-reactive protein continued to rise until day 6 to a maximum of 50.6 mg/dL.

On the fourth day, the rash was more confluent with target lesions. A skin biopsy revealed angiocentric dermatitis with moderate mononuclear perivascular infiltrate of the dermis and intravascular polymorph margination. Intravenous immunoglobulin (IVIG) 400 mg/kg/d was administered for 5 days. The liver was slightly homogeneously enlarged by abdominal ultrasonography. A transthoracic echocardiogram was normal. The respiratory condition did not improve, and inhaled nitric oxide was delivered for 6 days (maximum, 20 ppm; methemoglobin, <1%).

Blood, urine and bronchial secretion bacterial cultures remained negative. *Rickettsia conorii*, *Borrelia burgdorferi*, *Coxiella burnetii*, *Ehrlichia*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Leptospira*, *Pneumocystis carinii*, respiratory virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus and human immunodeficiency virus were excluded by serology and/or direct (antigen or nucleic acid) detection.

IgM and IgG antibodies against PB19 were positive (indirect immunofluorescence), and PB19 DNA by polymerase chain reaction (PCR) was detected in plasma (virus load, 4.8×10^4 genome copies/mL) bronchial secretions and skin biopsy (real time PCR; Real Art ParvoB19 RG).

An immunologic evaluation on day 6 showed decreased $CD8^+$ and $CD4^+$ lymphocytes, decreased IgG and total complement hemolytic activity. Antinuclear and cytoplasmic antineutrophil antibodies and circulating immunocomplexes were negative. She progressively improved, and ventilatory support ceased on day 13. The exanthema subsided after the first week. She was discharged from the Pediatric Intensive Care Unit after 16 days with no respiratory distress and no neurologic sequelae.

Five weeks after hospitalization, serum PB19 DNA remained detectable by PCR, (virus load, 10^3 genome copies/mL); IgM and IgG antibodies were positive. Immunologic evaluations (total lymphocyte and neutrophil counts, lymphocyte subpopulations, immunoglobulins including IgG subclasses and specific IgG antibodies, complement, phagocytosis and oxidative burst) 5 weeks and 3 months latter were normal.

PB19 DNA remained detectable by PCR during 6 months after acute disease.

The patient was enrolled in an investigation of the efficacy and safety of Dotrecogin Alfa (activated) in Paediatric Severe Sepsis (Eli Lilly and Co.).

DISCUSSION

This is a case of shock with multiple organ dysfunction syndrome and ARDS in a child with evidence of recent PB19 infection.

The detection of IgM and PB19 DNA in serum, skin tissue and bronchial secretions and the failure to detect other pathogens make it likely that parvovirus was the cause of disease, but proof of lung tissue infection was not possible.

The full spectrum of PB19 induced disease is not yet defined, and evidences of persistence, association with autoimmune diseases and atypical evolutions are increasing.[1,2] PB19 can infect and persist in both T and B lymphocytes, up-regulate cytokine expression and alter host cellular immunity.[2]

Treatment with IVIG in persistent infection results in decreased viremia and improvement of symptoms and has a potentially curative role.[1] We believe that IVIG was beneficial in this case because some apparently immune-related manifestations like the erythema improved.

Respiratory involvement to this degree caused by PB19 has been documented in only 2 immunocompetent women and in a pediatric case after heart transplantation.[3–5] A milder pleuropneumonitis was also reported in a healthy man.[6]

It is uncertain whether lung injury results from direct infection or from immune damage. The cellular receptor for PB19, erythrocyte P antigen, is expressed not only in erythroid cells but also in other tissues including the lung. Local viral replication might therefore represent a primary pathogenic mechanism.[2]

In our case as in the case reported by Wardeh and Marik,[3] the detection of DNA in respiratory tract secretions suggests a direct effect of the virus.

To the best of our knowledge, an association among human PB19 infection, multiple organ dysfunction syndrome and ARDS in immunocompetent children has not been previously reported.

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HYPOTONIC-HYPORESPONSIVE EPISODE IN A 7-MONTH-OLD INFANT AFTER RECEIPT OF MULTIPLE VACCINATIONS

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Abstract: A 7-month-old boy became difficult to arouse, was limp and had blue extremities 8 hours after immunization with intravenous poliovirus, diphtheria-tetanus toxoids-acellular pertussis, *Haemophilus influenzae* type b-hepatitis B virus and pneumococcal vaccines. The hypotonic-hyporesponsive episode had resolved by the time the infant was seen in an emergency department 1 hour later. The report describes hypotonic-hyporesponsive episode, encourages reporting of vaccine-associated adverse events and discusses prognosis and implications for subsequent immunization.

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The term hypotonic-hyporesponsive episode (HHE) was used to describe pallor, limpness, unresponsiveness, lethargy and irritability that occurred in 8 of >15,000 infants and children vaccinated with diphtheria-tetanus toxoids-whole cell pertussis (DTwP) vaccine in the late 1970s.[1] HHEs are recognized as rare and serious events after immunizations. Although HHEs have been reported after diphtheria, tetanus, *Haemophilus influenzae* type b (Hib) and hepatitis B virus (HBV) vaccines, >90% of reported episodes have been associated with pertussis containing vaccines.[2,3] The incidence of HHE is somewhat sketchy because the case definition of HHE is relatively new and a large portion of cases never seek medical attention. Reported incident rates range from 36–250 episodes per 100,000 after whole cell pertussis vaccine to 4–140 episodes per 100,000 after acellular vaccine.[2] It is clear, however, that the incidence of serious events, including HHE, has decreased significantly after the introduction of acellular pertussis vaccines.[4–6] Neither the pathogenesis nor the pathophysiology of HHE is known.

A case definition for HHE after immunization proposed in 1997 defines HHE as a sudden event within 48 hours of immunization characterized by all of the following: (1) limpness or hypotonia; (2) reduced responsiveness or hyporesponsiveness; and (3) pallor or cyanosis or failure to observe or to recall skin coloration.[7] A more extensive case definition, guidelines for data collection, analysis and presentation was published by the Brighton Collaboration in 2004.[2]

The purpose of this report is to present the case of a 7-month-old infant who experienced an HHE as defined above after the receipt of multiple vaccines, including acellular pertussis vaccine, to help providers recognize HHEs, encourage reporting and discuss prognosis and implications for subsequent immunization.

CASE REPORT

On the day of admission, R.T., a previously healthy 7-month-old boy, received intravenous poliovirus (Aventis), diphtheria-tetanus toxoids-acellular pertussis (DTaP) (sanofi pasteur), Hib/HBV (Merck) and pneumococcal conjugate (Lederle) vaccines at ~1:20 PM. Eight hours later, at ~9:30 PM, the patient was difficult to arouse, was limp, had blue extremities that were cool to touch and had a rectal temperature of 104.3°F. The patient arrived at a local emergency department at 10:25 PM. The patient was ill appearing and crying but consolable. The patient was easy to arouse, had appropriate tone and was no longer cyanotic. His temperature was 103.7°F (rectal), pulse was 200, a blood pressure was not recorded and his extremities were mottled and cool. White blood cell count was 7.2×10^9/L, hemoglobin 12.3 g/dL, hematocrit 35% and platelets 304×10^9/L. Serum electrolytes, blood urea nitrogen, creatine and glucose were normal. A roentgenogram of the chest was normal. The patient received 20 mL/kg normal saline and 100 mg/kg ceftriaxone iv. The patient's heart rate decreased after the fluid administration, and sinus tachycardia (140–190) was documented on a rhythm strip recorded during transport to Akron Children's Hospital.

At Akron Children's Hospital, vital signs were; temperature 100.6°F rectal, pulse 180/min, respiratory rate 30/min, blood pressure 101/57 mm Hg. Pulse oximetry was 100% on room air. The patient was responsive and had appropriate tone and color. The patient appeared ill and cried intermittently but did not appear toxic. The patient had a macular, erythematous rash on his cheeks, an erythematous macular rash with satellite lesions in the diaper area and scattered, elevated white plaques on the buccal mucosa and tongue. No local reaction to vaccine administration was noted. The remainder of the examination was normal.

The patient had no further HHE. Tests for respiratory syncytial virus, influenza, parainfluenza and adenovirus were negative. Serum electrolytes were normal. Blood cultures obtained after 1 dose of ceftriaxone were sterile. A second dose of ceftriaxone (50 mg/kg) was given 24 hours after admission. The patient defervesced within 40 hours of admission and remained afebrile for the remain-

der of the hospital course. The patient was treated for thrush and *Candida* diaper dermatitis and was discharged home with no no antibacterial agents prescribed after 62 hours of hospitalization. The patient continued to receive scheduled immunizations except pertussis. The patient has not had further adverse events associated with vaccine administration.

DISCUSSION

Our patient had an HHE that lasted for ~50 minutes occurring within 8 hours of receiving antigens from 15 different bacteria and viruses (intravenous poliovirus) (3), DTaP (3), Hib/HBV (2), and 7-valent pneumococcal conjugate vaccine (7). Statistically HHEs most often follow the administration of pertussis containing vaccine, but there is no way to know which antigen(s), if any, was responsible for this episode.

Most published reports on HHE focus on the incidence of episodes after immunization. There is less information about clinical findings and pathophysiology. In 1993, Blumberg et al[8] reported on 60 children 2 months–6 years of age who had seizures, HHE, high fever or persistent crying within 48 hours of receiving DTwP and were examined by one of the authors within 24 hours of the episode. In addition to examining the patients the authors collected blood and assayed for complete blood count and differential count, sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinene, calcium, phosphate, total protein, albumin, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase, cholesterol, triglycerides, uric acid, cortisol and pertussis toxin. The 14 patients with HHE ranged in age from 2 to 18 months. HHE began 0.2–25 hours after immunization and lasted for an average of 6 minutes (range, 8 seconds–4 hours). The mean temperature for HHE patients was 38.0°C (range, 36.9–40). All 14 children were normal on follow-up in 4–18 weeks. Pertussis toxin was not found in any of the 22 study patients tested (4 with HHE), and results of the other blood tests, including tests for an allergic etiology or glucose/insulin metabolism dysfunction, did not differ from normal in a clinically relevant way.[8] The authors suggested that HHE might represent a heterogeneous group of disorders ranging from syncopal episodes to atypical seizures with or without fever.[8] Similar symptoms are associated with syncope, seizures, breath-holding, aspiration, anaphylaxis, variations in sleep and superventricular tachycardia.[6]

Current recommendations of the Committee on Infectious Diseases of the American Academy of Pediatrics advise that the decision to administer additional doses of pertussis containing vaccine to children who have had serious adverse events like HHE after pertussis immunization be carefully considered.[9] To determine the risk of giving additional doses of pertussis containing vaccine to children who had HHEs after pertussis immunization, Goodwin et al[10] gave DTaP (55), DTwP (4) or diphtheria-tetanus toxoids vaccine (5) to 64 children who had previously had a HHE after receipt of a pertussis containing vaccine. Children were hospitalized for revaccination, observed in hospital for at least 6 hours after administration and followed up by telephone 24–72 hours after discharge from the hospital. None of the children had serious reactions after immunization, including HHE.

The primary care physician caring for the patient presented in this report elected to withhold future doses of pertussis vaccine. Available evidence suggests that it would be safe to give additional doses with caution.[10]

An ongoing study of the growth, health and neurodevelopment of 101 children with HHE in the Netherlands found the children to be in good health and developing normally 1.5 years after the episode.[7] That study also showed a "low rate" of recurrent HHE after subsequent doses of pertussis vaccine.[7] One hundred Swedish children who participated in a pertussis vaccine trial had HHEs and were subsequently evaluated at 18 months of age with standard tests to detect moderate to severe developmental problems. All were developing normally.[7]

It is important for providers who immunize infants and children to recognize and report unusual events occurring within 48 hours after immunization with killed vaccines and after the appropriate incubation period after giving live vaccines. Although it is often difficult to attribute a casual relationship between the administration of vaccines and an unusual event, any suspicious event should be reported.

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ADENOVIRUS, ADENO-ASSOCIATED VIRUS AND KAWASAKI DISEASE

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Abstract: Clinical similarities and shared seasonality suggested a relationship between adenovirus infection and Kawasaki disease. We performed adenovirus serology and quantitative polymerase chain reaction for both adenovirus and adeno-associated virus in patients with acute Kawasaki disease. No evidence was found to suggest a link between either virus and Kawasaki disease.

Key Words: adenovirus, adeno-associated virus, Kawasaki disease, neutralization titer, quantitative polymerase chain reaction
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Kawasaki disease is a self-limited acute vasculitis of children with a suspected infectious etiology[1,2] and defined seasonality.[3] In an attempt to find a clue for the infectious cause of Kawasaki disease, we examined the seasonality of different viruses in Japan. A strikingly similar bimodal seasonality was recognized for some serotypes of adenovirus. Adenovirus accounts for 5–10% of respiratory tract infections in children[4] and can mimic the clinical manifestations and laboratory abnormalities seen in Kawasaki disease.[5,6] In addition, adenovirus has been isolated from mesenteric lymph nodes of a child who died of Kawasaki disease, and a serologic survey implicated a relationship between adenovirus and Kawasaki disease.[7,8] Although adenovirus has been infrequently detected in acute Kawasaki disease patients by culture, we postulated that infection with a noncultivable adenovirus or antecedent adenovirus infection might be a trigger for Kawasaki disease. We analyzed patient samples using (1) broadly cross-hybridizing polymerase chain reaction (PCR) primers that amplify all 51 known adenovirus serotypes, (2) viral culture and (3) neutralization assays for the most common adenovirus serotypes [type 1 (Ad1), Ad2, Ad3, Ad4 and Ad7]. We also investigated possible involvement of adeno-associated viruses (AAVs), because AAVs depend on helper viruses such as adenovirus.[9] Currently there are 6 known human AAV serotypes with widespread seropositivity among human populations and with no known association to human disease.[10]

METHODS

The monthly incidence of Kawasaki disease in Japan was determined from hospital admission dates of 84,829 cases during a 14-year period (1987–2000) reported in the 16 Japanese nationwide surveys.[3] Monthly incidence of viral diseases in Japan during a 6-year period (1998–2003) was reported by district surveillance centers located in the 47 prefectures in Japan and posted on the Infectious Agent Surveillance Report website.[11] Seasonality was compared between Kawasaki disease and viral diseases including: Coxsackieviruses A2, A4–10, A12, A14, A16, A24, B1–6; echoviruses 1, 3, 5, 6, 9, 11, 13, 16, 18–20, 24, 25, 27, 30; influenza virus A–C; parainfluenza virus 1–3; respiratory syncytial virus; adenovirus 1–8, 11, 19, 31, 37, 40, 41; herpes simplex virus 1, 2, 6, 7; varicella-zoster virus; cytomegalovirus; Epstein-Barr virus; and parvovirus B19.

Kawasaki disease patients were enrolled during a 25-month period (February 2002–February 2004) at Children's Hospital and Health Center in San Diego, as described.[12] The research protocol was reviewed and approved by the Institutional Review Boards of the University of California San Diego and Children's Hospital and Health Center. Informed consent was obtained from the parents of all subjects. All patients were evaluated with serial echocardiograms. Measurements of the internal diameter of the coronary arteries by transthoracic echocardiography were interpreted as follows: dilated if z score is >2 and <3, ectasia if z score is >3 with uniform dilatation of vessel, aneurysm if focally dilated segment with z score is >3.[13] Illness day 1 was defined as the first day of fever. Clinical samples used in this study were collected within the first 14 days of fever onset and before intravenous immunoglobulin (IVIG) therapy. Nasopharyngeal swabs were cultured for adenovirus.[12] Standard adenoviral neutralization assays and colorimetric microneutralization for the 5 most common serotypes, 1–4 and 7,[14] were performed with the use of patient sera, with serial 2-fold dilutions starting at 1/10 and continuing through 1/80. Sera with a titer of 1/10 or greater were scored as positive.

At least 2 clinical samples from each patient, including throat swabs, sera or urine, were tested by TaqMan-quantitative PCR for adenovirus[12] and SYBR Green-quantitative PCR for AAV, with a GeneAmp 5700 thermocycler (PE Applied Biosystems). Degenerate primers [AAV1139F (5′-GSAAGATGACSGCCAAGGT-3′) and AAV1219R (5′-GGYTGYTGRTGYTCGAAGGT-3′)] were selected from a conserved region of the gene encoding the nonstructural protein Rep 78 of human AAV serotypes 1–6 (GenBank accession numbers: NC_002077; NC_001401; NC_001729; NC_001829; NC_006152; NC_001862).

Correlations between Kawasaki disease and adenovirus monthly incidence were determined with Pearson's correlation coefficient for calculation of r.

RESULTS

Although most of the viruses had a unique seasonal distribution (data not shown), only Ad 1–6 had the same seasonal pattern as Kawasaki disease (Fig. 1). Using different intervals to explore the correlation between adenovirus and Kawasaki disease monthly incidence, we found the highest correlation when a 1-month delay was introduced between the adenovirus and Kawasaki disease time series. Thus peak months for adenoviral infections were followed ~1 month later by a peak in Kawasaki disease incidence ($r = 0.84$, 0.77, 0.31, 0.37, 0.49 and 0.74 for each Ad 1–6 versus Kawasaki disease, respectively). The similarity between Ad 1–6 and Kawasaki disease seasonality in Japan prompted us to investigate a possible role of adenovirus as a trigger for Kawasaki disease in American children.

Nasopharyngeal viral cultures were collected before IVIG administration on illness day 3–14 (median, illness day 6) from 70 Kawasaki disease patients (median age, 28 months; range, 2–81 months). Of the 70 patients, 52 patients fulfilled 4 of 5 classic

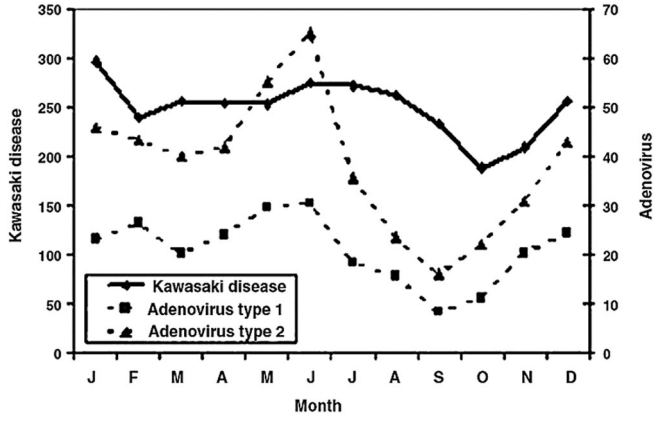

FIGURE 1. Comparison of average monthly incidence of Kawasaki disease in Japan during a 14-year period (1987–2000) with average monthly incidence of adenovirus types 1 and 2 isolated in Japan during a 6-year period (1998–2003). Letters on the horizontal axis indicate months of the year [January (J) through December (D)].

criteria[2] or 3 of 5 criteria with abnormal coronary arteries by echocardiogram. Of the remaining 18 patients with incomplete Kawasaki disease, 6 had coronary artery abnormalities. Overall 7 patients (10%) had coronary artery aneurysms, and 22 patients (31.4%) had coronary artery dilatation. Viral cultures were negative in 66 of the 70 Kawasaki disease patients. The viral isolates in 4 patients were respiratory syncytial virus (1), parainfluenza virus 3 (1) and adenovirus (2). Therefore adenovirus culture was negative in 97% of patients. Of the 2 adenovirus culture-positive patients, case 1 was a 21-month-old boy with fever, rash, nonexudative conjunctival injection and periungual desquamation during the convalescent phase. Case 2 was a 5-year-old boy with fever, rash, nonexudative conjunctival injection, strawberry tongue and cervical lymphadenopathy. Both responded to IVIG treatment with rapid resolution of fever, and neither developed coronary artery abnormalities.

Fifteen Kawasaki disease patients with negative adenovirus cultures were evaluated by adenovirus TaqMan PCR assay on at least 2 clinical samples (median day of collection, illness day 6.5), including throat swabs (15), serum (14) or urine (7). Fourteen patients had a negative PCR result. The throat swab from 1 patient collected on illness day 7 contained 800 adenovirus genome copies. This patient (case 3) was a 22-month-old girl with classic features of Kawasaki disease including prolonged fever, rash, nonexudative conjunctival injection, cervical lymphadenopathy, swollen hands and chapped red lips.

Because the seasonal peak of certain adenovirus serotypes preceded the seasonal peak for Kawasaki disease by 1 month, we postulated that these adenovirus serotypes could be a trigger for Kawasaki disease, in which case the viral neutralization titer would be positive at the onset of Kawasaki disease. We therefore measured adenovirus neutralization titers in the acute, pretreatment sera from children with Kawasaki disease. Results of adenovirus neutralization assays (mean day of serum collection, illness day 6) from 26 Kawasaki disease patients (median age, 14.5 months; range, 2–67 months) were as follows: Ad1, 11 of 26 (42.3%) positive; Ad2, 6 of 26 (23.0%); Ad3, 5 of 25 (20%); Ad4, 3 of 23 (13.0%); and Ad7, 11 of 26 (42.3%). Neutralization titers against any of the 5 adenovirus serotypes were undetectable in 4 of 26 patients (15.4%). Neither the number of positive serologies nor the titer was related to the illness day of serum collection.

The AAV-PCR assay was extremely sensitive, detecting 5 genome copies of an infectious plasmid clone of AAV type 2, pSub201.[15] None of the 36 samples from the same 15 acute Kawasaki disease patients described for the adenovirus TaqMan assay was positive for AAV.

DISCUSSION

Despite the striking similarities between Kawasaki disease and adenovirus infection,[5,6] viral culture, TaqMan PCR and neutralization assays failed to implicate adenovirus as a trigger for Kawasaki disease. Similarly no evidence for AAV infection was detected in acute Kawasaki disease patients.

Adenovirus was cultured from the throat of 2 Kawasaki disease patients (2.9% of subjects, cases 1 and 2). Although case 1 met only 3 of 5 diagnostic criteria,[2] the diagnosis of Kawasaki disease was further supported by the rapid defervescence after IVIG administration and the pathognomonic periungual desquamation in the convalescent phase. Case 2 had classic clinical and laboratory signs of Kawasaki disease with no respiratory symptoms. Thus the presence of adenovirus in these 2 patients may reflect shedding of virus from a prior, remote infection or coincidental infection, given that adenovirus infections are common in this age group[1,4] and share the same seasonality with Kawasaki disease.[3,11]

In the present study, Case 3, the only patient with positive PCR but negative culture had only 800 adenovirus genome copies/swab, which is much lower than amounts detected from the throats of children with acute adenovirus infection (10^6–10^7 copies/swab)[12] and likely below the threshold for a positive culture. This may indicate previous adenovirus infection with viral shedding rather than acute, active infection. Despite the documentation in other studies of asymptomatic shedding of adenovirus from the throat and in the feces,[1,4] we rarely detected adenovirus throat swab or nasopharyngeal swab. Our findings suggest that Kawasaki disease does not cause adenovirus reactivation.

Neutralizing antibody against adenovirus recognizes epitopes on both hexon and fiber polypeptides in a group- and type-specific manner, is detectable within days and continues to rise in titer for weeks postinfection.[16] The lack of a consistent pattern of neutralizing antibody argues against uniform remote exposure to adenovirus in Kawasaki disease patients. If more recent adenovirus infection were a trigger for Kawasaki disease, one would have expected to see higher antibody titers in patients sampled late in the course of Kawasaki disease. However, neither the prevalence of neutralizing antibodies nor the titer of these antibodies correlated with the illness day of the serum sample.

AAV is a member of the family Parvoviridae, genus *Dependovirus*, which depends for its replication on helper viruses, such as adenovirus. Unlike parvovirus B19, another member of Parvoviridae that causes erythema infectiosum and aplastic crisis, AAV has not been associated with human disease. Failure to find an AAV genome in Kawasaki disease patients by a sensitive PCR method argues against the hypothesis that AAV causes Kawasaki disease in a subset of genetically predisposed children.

Limitations of this study include the small number of subjects studied and that all patients were evaluated in 1 geographic location during only a 2-year period. Recognizing these limitations, we found no evidence that adenovirus or AAV trigger Kawasaki disease, the cause of which remains elusive.

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GROUP C AND G STREPTOCOCCAL DISEASE AMONG CHILDREN

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Abstract: Nine children with infections caused by group C and G streptococci were identified from 1995 through 2004. The children ranged in age from 12 to 18 years. The infections included 4 children with peritonsillar abscess/cellulitis and one child each with perirectal abscess, postoperative wound infection, ruptured appendix, septic arthritis and cellulitis/abscess. This study demonstrates the propensity of group C and G streptococci to cause disease in older children and at sites where the organisms reside normally.

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Group C and G streptococci are pathogens of humans and animals. They exist as normal flora in the pharynx, on the skin and in the gastrointestinal and female genital tracts and are associated most frequently with infections at these sites.[1] The spectrum of disease includes pharyngitis, sinusitis, cellulitis, bacteremia, puerperal sepsis, neonatal sepsis, pneumonia, meningitis, osteomyelitis, septic arthritis, endocarditis, pericarditis and endophthalmitis.[1] Group C and G streptococci account for 8.1 and 2.5%, respectively, of all acute infections caused by beta hemolytic streptococci.[2] The incidence of type-specific streptococcal disease is age-dependent. For example, group B streptococcal disease is almost exclusively a disease of infants, whereas group A streptococcal disease is mostly a disease of school children.[3,4] In contrast, group C and G streptococcal disease occurs predominantly among adults.[3] The purpose of this report was to describe group C and G disease among children.

METHODS

The hospital records were reviewed for the 10-year period of January 1, 1995, through December 31, 2004. Cases were identified with the ICD-9 codes 04103 for group C streptococcus and 04105 for group G streptococcus.

RESULTS

Nine cases were identified; 4 children had group C disease and 5 children had group G disease (Table 1). The children ranged in age from 12 years, 2 months to 18 years, 5 months. There were 5 girls and 4 boys. There were 8 white children and 1 black child. The white blood cell count was elevated in every case.

Group C Disease. Two of the children had left-sided peritonsillar abscesses. Aspiration of the abscesses yielded 4–6 mL of pus. Group C streptococci were isolated exclusively. Both children were treated briefly with intravenous clindamycin or ampicillin-sulbactam and switched to oral amoxicillin-clavulanate to complete a 10-day course. One child had a perforated appendix. Cultures of the peritoneal fluid yielded group C streptococcus exclusively. The appendix was removed laparoscopically. The child was initially treated with intravenous ampicillin, gentamicin and metronidazole for 7 days and then sent home and treated with intravenous imipenem for 3 additional days. The fourth child with group C streptococcal disease had sacroileal septic arthritis. Two blood cultures yielded group C streptococcus. He was treated with intravenous oxacillin for 7 days and treated at home with intravenous cefazolin for an additional 21 days. All of the children responded well and none developed complications.

Group G Streptococcus. Two of the children had left-sided peritonsillar abscesses/cellulitis. Group G streptococcus was isolated from 3 mL of aspirated pus from one child and from a throat culture from the child with cellulitis. Both children were treated with 3 days of intravenous clindamycin, followed by 7 days of oral clindamycin, to complete 10 days of therapy. One child had an abscess and cellulitis in his left calf after a sports injury. The abscess was incised and drained. Culture of the pus yielded group G streptococcus. He was treated initially with 1 day of intravenous oxacillin followed by 9 days of cephalexin. One child developed an abscess 2 weeks after a pilonidal cyst was excised and closed. Group G streptococcus was isolated from the pus from the abscess. The child was treated with intravenous amoxicillin–sulbactam for 5 days followed by treatment with ampicillin–clavulanate for 5 days. Another child had a perirectal abscess. The abscess was incised and drained. A Gram stain of the pus demonstrated Gram-positive cocci in chains and Gram-negative rods. The culture yielded group G streptococcus and *Escherichia coli*. The child was treated with intravenous ampicillin, gentamicin and metronidazole for 5 days. However, the child remained hospitalized for 3 weeks because of slow healing of the wound and prolonged pain.

DISCUSSION

Our experience is that group C and G streptococci are infrequent causes of disease in children. The 2 serotypes accounted for 9 infections during a 10-year period. Both serotypes caused peritonsillar disease in 4 of 9 children. While both C and G streptococci are considered infrequent causes of pharyngitis, both serotypes have been implicated in peritonsillar abscesses.[4–9] Three other children had infections related to the gastrointestinal tract and one had an infection of the skin. Thus, 8 of 9 infections occurred at sites where these streptococci normally reside.[1]

TABLE 1. Clinical Data

Patients	Age	Sex	Race	Diagnosis	Admission Temperature (°C)	White Blood Cell Count (Cells/mm^3)
Group C						
1	17 yr 9 mo	F	W	Peritonsillar abscess	37.4	13,300
2	17 yr 9 mo	M	W	Peritonsillar abscess	38.0	19,400
3	15 yr 9 mo	M	B	Septic arthritis	38.9	24,200
4	12 yr 2 mo	F	W	Perforated appendix	38.3	19,000
Group G						
1	15 yr 1 mo	F	W	Peritonsillar abscess	37.0	13,200
2	14 yr 4 mo	F	W	Abscess/cellulitis	37.2	23,900
3	17 yr 2 mo	M	W	Skin abscess	38.2	14,200
4	18 yr 2 mo	F	W	Postoperative infection	39.6	33,000
5	18 yr 5 mo	M	W	Perirectal abscess	37.5	29,500

The antibiotic of choice for both streptococci is penicillin. Most microbiology laboratories, including ours, do not routinely test susceptibility of these pathogens. Occasional strains of group C streptococci have been observed to be tolerant to penicillin. The clinical significance of tolerant strains is questionable. In the present report, a number of different antibiotics were used and clinical responses were good in every case. Only one child with a postoperative wound infection had a prolonged hospitalization, possibly resulting from the location of the wound over the distal sacrum.

The age distribution of the cases confirmed the reported older-age distribution of group C and G streptococci; all 9 children in the present report were older than 12 years of age,[3,4] and the median age of the cases was 17 years, 2 months. There is no clear explanation for this age distribution.

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HUMAN CORONAVIRUS NL63 ASSOCIATED WITH LOWER RESPIRATORY TRACT SYMPTOMS IN EARLY LIFE

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Abstract: Coronavirus NL63 has been identified as a new member of the coronavirus genus, but its role as a cause of respiratory disease needs to be established. We studied the first episode of lower respiratory tract symptoms in a cohort of healthy neonates. NL63 was identified in 6 (7%) of 82 cases and was as frequent as other coronaviruses (9%). NL63 was recovered at the onset of symptoms and was cleared within 3 weeks in half of the cases. Our data suggests that coronavirus NL63 causes lower respiratory tract symptoms and is acquired in early life.

Key Words: coronavirus, coronavirus NL63, respiratory viral infections, infants, respiratory tract infections

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Human coronaviruses cause seasonal infections in the community. They lead to upper respiratory illnesses, but also to lower respiratory tract infections.[1] In addition to OC43 and 229E, 2 new members of this family have been identified recently in humans: the severe acute respiratory syndrome coronavirus; and NL63.[2] The impact of the former is limited to special epidemiologic circumstances. Initial studies leading to the identification of NL63 suggested that most infections occur in very young children, before 1 year of age.[2,3] However, the symptoms associated with NL63 infections have not been well described and our understanding of its epidemiologic pattern remains limited. Serologic studies are not yet available, but this approach might be limited by cross-reactions with other coronaviruses or previous infections, particularly if these infections are frequent and acquired in early life. Thus the role of NL63 compared with OC43 and 229E needs to be established by appropriate diagnostic tools that can differentiate each member of this family.

To assess the role of NL63 in respiratory tract infection, we analyzed the first episode of lower respiratory tract symptoms in a prospective birth cohort of healthy neonates.[4]

MATERIALS AND METHODS

Neonates enrolled in the study were followed for any respiratory event and/or fever episode during their first year of life. Clinical symptoms were assessed by a weekly standardized interview of parents.[5] A lower respiratory tract symptom episode was defined as more than 2 days with symptoms of lower airway disease

(cough or wheeze) and concomitant fever (>38°C), acute rhinitis, otitis or tonsillitis. A nasopharyngeal swab was collected at the first episode and stored within hours at −80°C. Specimens were thawed and analyzed by reverse transcription-polymerase chain reaction for NL63, OC43 and 229E, as well as for all other respiratory viruses that commonly infect humans.[6] These assays are specific for each coronavirus and have been described in detail previously.[6] The ethics committee of the University of Berne approved the study and written informed parental consent was obtained for all infants.

RESULTS

We analyzed the first episode of lower respiratory tract symptoms in 82 infants. Coronaviruses were identified in 13 (16%) cases at the onset of lower respiratory tract symptoms: NL63 in 6 cases (46%); OC43 in 5 cases (38%); and 229E in 3 cases (23%). Dual viral respiratory infections were documented in 2 cases: OC43 and NL63 in one; and rhinovirus and NL63 in the other. Coronavirus infections occurred at a median of 5.7 months of age (range, 0.7–11.4 months) and predominantly during the cold months (Table 1). Median duration of symptoms was 2 weeks (range, 1–4 weeks). In addition to a cough or wheeze, all infants had an acute rhinitis; 5 had fever and 2 were treated with antibiotics. Disturbed sleep (due to cough and wheeze) and/or impaired daily activity (play or feeding problems) were observed in 9 cases; none was hospitalized. Five of the 13 cases, including 2 NL63 cases, had never experienced previous respiratory symptoms. Cough or wheeze was preceded by upper respiratory tract symptoms in 4 of 6 of the NL63 infections. In 5 infants, coronaviruses, including NL63 in 3, were still detected in follow-up samples 3 weeks after the acute episode.

DISCUSSION

In this study, we show that NL63 is temporally associated with lower respiratory tract symptoms in infants. The presence of coronavirus NL63 was concomitant to an acute episode of cough or wheeze and rhinitis, as well as disturbances in life activities, and led to a clinical picture similar to that induced by other members of this family. Symptoms were limited to 2 weeks in most cases. As 2 of 6 NL63-positive infants had never experienced any previous respiratory symptoms, and as the upper respiratory symptoms in the other 4 NL63-positive infants immediately preceded the studied period, the recovery of NL63 in the respiratory samples of these infants was not a remnant of a previous upper respiratory infection. In addition, the viral shedding was documented only at the peak of the symptoms and, in half of the cases, the virus was cleared concomitant to symptom resolution. Taken together, these observations support our conclusion that NL63 should be considered as a cause of lower respiratory illness in early life. Adding this agent to the list of respiratory viruses will decrease the proportion of respiratory diseases of unknown etiology.

However, our study has some limitations. By selecting a population with lower respiratory tract symptoms, we do not describe the whole spectrum of diseases associated with coronavirus NL63 infection. Indeed, a substantial number of these infections might cause symptoms limited to the upper respiratory tract only, but this needs to be addressed in additional community-based studies. Since we searched for coronaviruses in the upper respiratory tract only, it seems likely that cough and/or wheeze were not always related to the presence of the virus itself in the lower respiratory tract, but also to the release of various mediators following the upper respiratory tract infection. In the population and seasons studied, NL63 (recovered in 7% of all cases) was as frequent as OC43 and 229E, suggesting that it circulates in the community in an endemic fashion.

Our findings are consistent with recent reports in which coronavirus NL63 has been recovered in 2–3.6% of respiratory specimens in mixed populations of children, adults and elderly persons suffering from acute respiratory tract infection.[7–10] A recent report in children with respiratory diseases in Connecticut[11] showed that this virus may account for a significant proportion (up to 8%) of respiratory diseases in infants. Given the known ability of coronaviruses to cause pneumonia, our results also suggest that NL63 might be considered as a potential cause of complications in immunocompromised children or children with chronic pulmonary diseases. Cases of severe lower respiratory diseases, including bronchiolitis, have been described in hospitalized children.[9] At this time, NL63 seems to be an infrequent cause of severe lower respiratory tract complications in adults,[6] suggesting that most adults have been exposed at a young age to the virus.

Among the 13 neonates studied, approximately one-third were still positive for viral coronavirus RNA after 3 weeks, sug-

TABLE 1. Clinical Features of Infants (n = 13) With Coronaviruses OC43, 229E or NL63 as the First Cause of Lower Respiratory Tract Symptoms

Infant ID	Age (mo)	Previous Respiratory Symptoms*	Season	Virus Type	Preceded by Upper Respiratory Symptoms†	Cough or Wheeze	Fever	Sleep Disturbed	Daily Activities Disturbed	Antibiotic Use	Symptom Duration (wk)	Coronavirus Shedding at 3 wk
1	7.4	Yes	Spring	E229	No	Yes	No	Yes	Yes	No	4	No
2	6.3	Yes	Spring	NL63	Yes	Yes	Yes	No	No	No	3	No
3	11.1	Yes	Autumn	NL63	Yes	Yes	Yes	Yes	Yes	No	1	No
4	6.8	No	Winter	OC43 NL63	No	Yes	No	Yes	No	No	4	0C43 NL63
5	0.7	No	Summer	OC43	No	Yes	No	Yes	No	No	2	No
6	1.9	No	Autumn	OC43	No	Yes	No	No	Yes	No	1	OC43
7	5.7	Yes	Winter	NL63	Yes	Yes	Yes	Yes	Yes	Yes	2	NL63
8	5.6	Yes	Spring	NL63‡	Yes	Yes	No	No	No	No	2	No
9	4.8	Yes	Spring	OC43	No	Yes	No	No	Yes	No	1	OC43
10	1	No	Winter	NL63	No	Yes	No	Yes	Yes	No	1	NL63
11	4.3	Yes	Autumn	E229	No	Yes	No	No	No	No	1	No
12	11.4	Yes	Spring	OC43	No	Yes	Yes	Yes	Yes	No	1	No
13	8	No	Winter	E229	No	Yes	Yes	No	No	Yes	2	No

*Any episode of upper and/or lower respiratory symptoms or fever preceding the present episode of respiratory tract symptoms during the first year of life.
†Cases in whom upper respiratory tract symptoms preceded lower respiratory tract symptoms.
‡Dual infection with rhinovirus.

gesting that prolonged viral shedding may occur. A dual infection (NL63 and OC43) was observed in 1 case for at least 3 weeks. This could be significant given the replication strategies used by coronaviruses and their potential ability to recombine, and frequent and prolonged dual infections could lead to the emergence of new recombinant variants.

In conclusion, our data suggest that coronavirus NL63 is as frequent as the previously known human coronaviruses OC43 and 229E and can be associated with lower respiratory tract symptoms in infants.

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CHANGES IN LABORATORY FEATURES OF 192 CHILDREN WITH IMPORTED FALCIPARUM MALARIA TREATED WITH QUININE

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Abstract: Little is known about changes in laboratory values of children with imported falciparum malaria. Of 192 children, 69% had parasitemia of 2% or less and 64% had platelets $<150 \times 10^9$/L. In 20%, parasite counts rose within 12–24 hours of starting treatment before falling, whereas the platelet counts dropped in 45% but returned to normal levels within 5 days. Hemoglobin values were <10 g/dL in 31% at presentation and dropped in 61% at 5–21 days after treatment, but did not fall below 6.8 g/dL in any case. Blood cultures were negative in all children. Hyponatremia (n = 16), jaundice (n = 4) and hypoglycemia (n = 0) were uncommon. Thus most children presented with abnormal laboratory values, which initially worsened in a significant proportion, but none required active intervention once therapy was initiated.

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Malaria is one of the major causes of morbidity and mortality worldwide, with reported death rates ranging from 1.5 to 2.7 million a year; children younger than 5 years of age account for more than a million cases.[1] In nonendemic areas, imported malaria cases continue to rise as travel to malaria-endemic areas becomes more accessible and affordable.[2] The United Kingdom has one of the highest incidences of imported malaria among industrialized countries, with more than 2000 cases reported annually.[2,3] Children account for around 15% of these cases, which occur mainly in those traveling to their parents' country of origin without adequate antimalarial prophylaxis.[2]

In contrast to *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale* infections, children with *Plasmodium falciparum* malaria can deteriorate rapidly with shock, renal failure, convulsions, coma and death within hours.[2,4] Because children are less likely than adults to report specific symptoms and because they have many febrile illnesses, malaria may not be suspected, resulting in delayed treatment.[2] *P. falciparum* accounts for almost all the morbidity and mortality associated with imported malaria in adults and children.[5] In the United Kingdom, of around 2000 annual cases reported to the Malaria Reference Laboratory, the proportion of imported malaria cases caused by *P. falciparum* has risen substantially in the past 30 years, from 17% in 1977 to 40% in 1987 and 77% in 2001.[5]

The Royal London and Newham General Hospitals in East London serve an ethnically diverse population. The east end of London has high unemployment, crime, birth rates and infant mortality, as well as poor education and overcrowding. About half of the population is white and the rest belong to several different ethnic groups, primarily from sub-Saharan Africa and the Indian subcontinent. We have previously reported epidemiologic features of 211 children with imported malaria in East London.[6] In this study, we reviewed the hematologic, biochemical and microbiologic features of children with imported malaria caused by *P. falciparum* and changes that occurred in these laboratory values with quinine therapy.

METHODS

Children diagnosed with falciparum malaria between January 1996 and December 2001 were identified from hospital discharge data and cross-checked with the hematology database for positive malaria parasite slides. As a retrospective chart review, this study did not require ethical approval by local or national research ethics committees. *P. falciparum* malaria was diagnosed by examination of thick and thin blood films, which were later reviewed and confirmed by the National Malaria Reference Laboratory in London. Severe malaria was defined according to the World Health Organization criteria.[4] Children diagnosed with malaria were treated according to the hospital protocol based on local and national recommendations.[2]

All children were admitted for at least 12 hours. Blood tests were performed and/or repeated only where there was a clinical indication, and follow-up tests were requested at the discretion of the attending pediatrician. Thus children with uncomplicated malaria with a low parasitemia and normal hemoglobin and platelet concentrations on admission were unlikely to have a repeat blood test, while those with a high parasitemia, anemia or thrombocytopenia were more likely to have multiple blood tests. Children with uncomplicated malaria, a parasitemia of 2% or less and able to tolerate oral medication received oral quinine. Intravenous quinine (a loading dose of 20 mg/kg quinine dihydrochloride salt followed by maintenance doses of 10 mg/kg every 8 hours) was used in children with parasitemia of >2% or with severe malaria until the parasite count dropped to <1%, when treatment was changed to oral quinine. Treatment duration was 7 days with 1 dose of sulfadoxine-pyrimethamine (Fansidar) on the last day of treatment.

A predefined questionnaire was used to extract information from the notes, including demographic details, patient characteristics, laboratory results and outcome. Data were entered into Microsoft Excel (Office for Windows XP, 2002) and analyzed with Stata version 7. Proportions were compared with the use of the χ^2 test or Fisher's exact test, while continuous variables were compared using Student's tests; all P values were 2-tailed.

RESULTS

Patient Characteristics, Clinical Features and Treatment. The median age of the 192 children with *P. falciparum* malaria was 9 years (interquartile range, 4.9–11.8 years; range, 1.1–14.8 years) and 53% were male. Most children (89%) were residents of the United Kingdom and had traveled to a malaria-endemic area. Of these, antimalarial prophylaxis was taken by 37% of children and only 13% took prophylaxis according to recommended guidelines.[2] All cases were acquired in Africa, mainly Nigeria (59%), Ghana (11%) and Uganda (6%). Fifteen children (8%) had severe malaria, including hyperparasitemia (parasitemia >5%; n = 6), convulsions (n = 4), jaundice (n = 4), acute renal failure (n = 3) and severe anemia (hemoglobin <5 g/dL; n = 3). The clinical features of the children in this study have been described previously.[8]

Diagnosis was delayed in 58 children (30%) by at least 1 day. There was no difference in the country traveled, antimalarial prophylaxis, admission hemoglobin, or white blood cell, platelet or parasite counts. However, the proportion of children presenting with severe malaria was doubled in children in whom the diagnosis was delayed [7 of 58 (12%) versus 8 of 134 (6%)] although this was not statistically significant (χ^2 2.1; $P = 0.15$). Children with delayed diagnosis were more likely require admission to the intensive care unit [3 of 58 (5%) versus 1 of 134 (0.7%); χ^2 3.9; $P = 0.049$].

Intravenous quinine was administered to 80 children (42%) for 1 (n = 23), 2 (n = 29), 3 (n = 16) or more (n = 12) days, followed by oral quinine to complete a minimum 7-day course. All children received sulfadoxine–pyrimethamine (Fansidar) at the end of quinine therapy. No significant side effects or toxicity was recorded with intravenous or oral quinine. One child with an initial parasitemia of 1% relapsed after 21 days, but responded to another course of oral quinine. The relapse was thought to have occurred because of poor compliance to antimalarial therapy. The median duration of in-patient stay was 2 days (IQR 1–4 days; range, 0–20 days) and all children improved without sequelae. The admission laboratory values of children with falciparum malaria are summarized in Table 1.

Parasitemia. Most children (69%) presented with parasitemia of 2% or less and the 6 patients with parasitemia >5% (range, 8.5–27.6%) responded to quinine without the need for exchange transfusion. The parasite count dropped within 12–24 hours of starting treatment in 111 of 139 children (80%) who had a repeat test, but rose by a median of 1% (IQR 0.5–4.2%; range, 0.3–20.4%) in 28 cases (20%) before falling. The parasite count rose by more than 5% in 4 children (7% to 27.6%, 6% to 15%, 4% to 15% and 3% to 11%, respectively), but subsequently dropped as treatment progressed. The parasite count was more likely to rise in children with severe malaria [7 of 15 (47%) versus 21 of 124 (17%) cases; χ^2 7.4; $P = 0.007$].

Hemoglobin Values. A third of the children (31%) had anemia (hemoglobin <10 g/dL) at presentation and the 3 cases of severe anemia each required one blood transfusion. Hemoglobin values dropped by a median of 0.9 g/dL (IQR 0.1–3.2; range, 0.1–4.1 g/dL) in 54 of 89 children (61%) who had a follow-up test at 5–21 days after treatment. In only 2 cases (2.2%) did the hemoglobin drop by >2.5 g/dL, from 13.8 to 9.7 g/dL and 9.9 to 6.8 g/dL; these children had parasitemia of 4 and 5%, respectively, on admission. On discharge, anemia was the most common problem, occurring in 20 children and requiring supplemental iron treatment in one-half of them.

Platelet values. Thrombocytopenia (platelets $<150 \times 10^9$/L) was present in 123 children (64%), including 7 of 15 (47%) with severe malaria. Thrombocytopenia was associated with parasite count only, with a median platelet count of 127×10^9/L (IQR $90–198 \times 10^9$/L) in 133 children with parasite count of 2% or less compared with 93×10^9/L (IQR $58–140 \times 10^9$/L) in 59 children with parasitemia >2% ($P < 0.001$). None had clinical or laboratory evidence of abnormal bleeding. The platelet count dropped further in 63 of 139 children (45%; including 39% of 98 children with thrombocytopenia at presentation and 67% of 15 children with severe malaria) who had a repeat test 12–24 hours after starting treatment. Of the 63 children whose platelet count fell, the median drop was only 17×10^9/L (IQR $4–32 \times 10^9$/L; range, $1–148 \times 10^9$/L). In only 9 cases (7 were not thrombocytopenic at diagnosis) did the platelet level drop by $>50 \times 10^9$/L and in none did the platelet level fall below $50 \times$

TABLE 1. Laboratory and Microbiology Parameters of 192 Children With Imported Falciparum Malaria

Parameter	Cases (n)	Children Tested (n)	%
Hemoglobin concentrations (g/dL)			
>10	130	192	67.7
5–10	59	192	30.7
<5	3	192	1.6
Platelet concentrations ($\times 10^9$/L)			
>400	6	192	3.1
150–400	64	192	33.3
20–149	118	192	61.5
<20	4	192	2.1
White blood cell counts ($\times 10^9$/L)			
>15	6	192	3.1
5–15	140	192	72.9
<5	46	192	24.0
Parasite %			
>5	5	192	2.6
2.1–5	54	192	28.1
1–2	34	192	17.7
<1	99	192	51.6
Sodium <130 mmol/L	16	142	11.3
Creatinine >200 μmol/L	3	142	2.1
Bilirubin >25 mmol/L	19	108	17.6
Aspartate transaminase >40 IU/L	39	108	36.1
Glucose <2.2 mmol/L	0	192	0
Erythrocyte sedimentation rate >30 mm/h	30	30	100
C-reactive protein >30 mg/L	30	30	100
Blood cultures	0	192	0
Cerebrospinal fluid cultures	0	6	0

10^9/L. The platelet count of all 65 children with thrombocytopenia who had repeat test 5–17 days after starting treatment had risen above 150×10^9/L by the fifth day.

Biochemistry, renal and liver function. None of the 11 children with hyponatremia (sodium <130 mmol/L) presented with convulsions. The 3 children with acute renal failure had other features of severe malaria (2 had convulsions and 1 was drowsy) and all responded to fluid management and antimalarial therapy without the need for dialysis or filtration. Liver function tests were abnormal in 36% of children tested. None of the children had hypoglycemia at presentation or during treatment. All values returned to normal after antimalarial treatment without active intervention.

Microbiology. Blood cultures were taken in all children at presentation and none was positive (0%, 97.5% confidence interval, 0.0–1.9%). Lumbar punctures performed in 6 children with convulsions (n = 4) or excessive drowsiness (n = 2) were sterile in all cases.

DISCUSSION

Unlike many previous studies that included a large number of recent immigrants, almost 90% of children in our study were residents in the United Kingdom. Only those with falciparum malaria were included because *P. falciparum* is almost exclusively responsible for the severe morbidity and mortality associated with malaria.[5] Our retrospective study confirms that quinine with single dose of sulfadoxine–pyrimethamine is safe and effective against falciparum malaria. Most large studies on falciparum malaria have been reported in developing countries where malaria is endemic. Severe anemia, reported in 5–15% of those requiring hospital admission,[7,8] is often due to a combination of acute and chronic malaria infection, sickle cell disease, iron deficiency, malnutrition and other concurrent infections, particularly due to intestinal helminthes.[9,10] Thrombocytopenia is present in 50–65% of children and is not associated with bleeding problems.[11] Leukocytosis, which occurs in up to 20% of children, is an independent feature of malaria and associated with severity and death.[11] In children with severe malaria, leukocytosis is also associated with concurrent bacteremia, which occurs in around 2–10% of children.[12]

In contrast, there is a paucity of robust data for imported malaria, mainly because most studies have reported small numbers of cases.[13–16] In the North American reports of children with imported malaria (20–52 children in each study), anemia was present in 50–100% of children, thrombocytopenia in 45–71%, leucopoenia in 19–30%, hyperbilirubinemia in 30–50%, and a raised alanine or aspartate transaminase level in 25–40%.[13–16] Viani and Bromberg[16] also reported that 5 of their 20 children (25%) had hyponatremia, of whom one presented with seizures. Our results are similar to these studies, with anemia occurring in 31%, leucopoenia in 24%, thrombocytopenia in 64%, hyponatremia in 11%, hyperbilirubinemia in 18%, and raised aspartate transaminase concentrations in 36%. Leukocytosis was uncommon in our patient population and has rarely been reported in the previous studies.

In addition to the above results, several other findings from our study have not previously been reported, including the low risk of concurrent bacteremia and changes in hematologic and biologic values with treatment. The number of children reported in previous studies has been too small for authors to report negative findings, such as negative bacterial cultures, with statistical confidence. In their series of 52 children, however, McCaslin et al.[14] reported that one child had *Klebsiella pneumoniae* bacteremia and died, while cerebrospinal cultures of 6 children presenting with seizures were negative, as were all urine and stool cultures. In our study, none of the 192 children had concurrent bacteremia or meningitis, even among those who presented with severe or cerebral malaria, although there were only a few children in the latter group. This is important because concurrent bacteremia has been reported in 2–7% of children with malaria in endemic areas and children with severe malaria are usually treated empirically with antibiotics on admission.[11,12] Possible explanations for the higher incidence of concurrent bacteremia in malaria-endemic areas include poor socioeconomic status, overcrowding, delay in seeking medical help, lack of routine immunization, malnutrition and HIV infection.[17]

Because many of the children were admitted to the pediatric ward for at least 1 day and usually followed-up after discharge, sequential blood results were available for a significant number of our patients. Although abnormal hematologic and biochemical abnormalities are consistently reported in children with malaria, to date there have been no studies to determine the course of these abnormal values with treatment. Although not all children in our study received multiple blood tests, the decision to repeat a blood test was based on clinical assessment.

Our results showed that the platelet counts dropped in almost half of the children within 12–24 hours of starting treatment, whereas the parasite count rose in 20%. In many cases, this resulted in a longer in-patient stay and more blood tests. Furthermore, the hemoglobin level also dropped in almost two-thirds of patients after treatment completion. In all cases, however, the changes were never significant enough to warrant active intervention. The platelet counts normalized within 5 days, the parasitemia resolved, and the hemoglobin level stabilized. It is reassuring to note there were no fatalities in our study, which is consistent with other recent U.K.,[6] European[18] and American[13–16] pediatric reports.

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CHRONIC GRANULOMATOUS DISEASE PRESENTING WITH EOSINOPHILIC INFLAMMATION

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Abstract: Chronic granulomatous disease (CGD), a rare immunodeficiency, typically presents with recurrent infections caused by catalase-positive organisms. We report 2 patients with CGD who presented with eosinophilic inflammatory conditions recognized before the diagnosis of CGD. Both patients had significant urologic disease. Physicians should be aware of the association of CGD with eosinophilic inflammatory conditions.

Key Words: chronic granulomatous disease, eosinophilia, inflammation

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Chronic granulomatous disease (CGD) is a rare, inherited immunodeficiency characterized by an abnormal neutrophil respiratory burst.[1,2] Most children with CGD present in early childhood with recurrent infections caused by catalase-positive organisms. We describe 2 patients with CGD who presented with eosinophilic inflammatory conditions. One of the boys initially presented with eosinophilic cystitis and vesicoureteral reflux and later was diagnosed with CGD after developing *Achromobacter xylosoxidans* lymphadenitis. The second patient was diagnosed with eosinophilic gastroenteritis and later with CGD after an *Aspergillus* chest wall infection.

CASES

Case 1. A 1-year-old boy presented with recurrent episodes of apparent dysuria with micturition; repeat urine cultures were negative. A voiding cystourethrogram revealed grade II vesiculoureteral reflux with mild right-sided pelviectasis. He was given trimethoprim-sulfamethoxazole for urinary tract infection prophylaxis. One year later, dysuria returned; urine cultures were again negative. Cystoscopy revealed a trabeculated bladder wall. Bladder biopsy showed eosinophilic cystitis. He was treated with hydroxyzine with some symptomatic improvement, although intermittent symptoms of dysuria continued.

At 3 years of age, he presented with bilateral cervical tender lymph node swelling and fever to 104°F. He was diagnosed with lymphadenitis and failed therapy with multiple oral and intramuscular antibiotics including cefprozil, clarithromycin and ceftriaxone. A computed tomography scan of the neck revealed bilateral anterior and posterior cervical lymphadenopathy without abscess. A chest radiograph was normal, and an abdominal computed tomography scan revealed no further lymphadenopathy. A bacterial culture obtained from a cervical lymph node biopsy specimen was positive for *Achromobacter xylosoxidans*; mycobacterial, fungal and viral cultures were negative. There was remarkable clinical improvement within 3 days of starting intravenous trimethoprim-sulfamethoxazole. A flow cytometry test for X-linked chronic granulomatous disease was positive.[3] A younger, healthy brother was found to have the disease as well.

Case 2. A 4.5-year-old Hispanic boy presented with a painful mass on the left chest for 3 days and cough for 3 weeks. He had no fevers or weight loss. Past medical history was significant for eosinophilic colitis diagnosed by colonic biopsy since age 1 year when he presented to an outside hospital with vomiting and bloody diarrhea, requiring parenteral nutrition for failure to thrive. At presentation, he was taking prednisone 5 mg every other day for eosinophilic colitis and Singulair and ferrous sulfate for presumed iron deficiency anemia. Weight was 14.2 kg ($<5\%$), and height was 93 cm ($\ll 3\%$). Vital signs were normal. The left-sided chest wall mass was 4.5 × 4 cm, firm and nontender. There was no overlying erythema or warmth. Lung sounds were coarse bilaterally. There was no hepatosplenomegaly.

Complete blood count showed a white blood cell count of 26,200/μL with 21% lymphocytes, 60% neutrophils, 13% band forms and 3% eosinophils; hemoglobin 7.1 g/dL; and platelets of 808,000/μL. Mean corpuscular volume was 52.7 fL, and red blood cell distribution width was 21.2%. Erythrocyte sedimentation rate was 93 mm/hour. Liver chemistries were normal.

Chest radiography demonstrated a wide mediastinum and left-sided soft tissue density. Computed tomography demonstrated a 4.6- × 3.7-cm lymph node in the anterior mediastinum and a large chest wall mass that invaded bony structures. Biopsy and debridement of the anterior chest wall mass were performed. Purified protein derivative skin testing was negative. Cultures were negative for mycobacteria, as were aerobic and anaerobic bacterial cultures. Fungal cultures grew *Aspergillus fumigatus*. Therapy was changed to amphotericin 1 mg/kg for 2 weeks and then itraconazole for 6 weeks. Flow cytometry testing confirmed X-linked chronic granulomatous disease[3]; the patient was given interferon-γ and trimethoprim-sulfamethoxazole therapy. Prednisone therapy was discontinued, and repeat colonoscopy showed normal histology.

Four months later, he developed abdominal pain. Abdominal ultrasound showed marked bilateral hydronephrosis and dilatation of the proximal ureters. Computed tomography showed diffuse retroperitoneal soft tissue thickening and lack of intravenous contrast flow in the distal ureters, suggesting external compression of the ureters. Bilateral nephrostomy tubes and ureteral stents were placed, and retroperitoneal mesenteric lymph nodes were biopsied. Pathology of a retroperitoneal node showed granulomata, histiocytes, giant cells and a large number of eosinophils. All bacterial, fungal and mycobacterial cultures were negative. Prednisone and itraconazole prophylaxis was begun and was continued until hydronephrosis resolved and ureteral stents were removed upon resolution of the hydronephrosis.

DISCUSSION

CGD is a rare, inherited immunodeficiency characterized by susceptibility to catalase-positive bacterial and fungal infections, as well as granulomas in many organs. The biochemical defect of CGD resides in the NADPH oxidase system, leading to an abnormal respiratory burst that impedes killing of catalase-positive organisms during phagocytosis.[1] About 60–70% of patients with CGD have an X-linked mutation; the rest derive from a variety of autosomal recessive defects in the NADPH oxidase complex.[1,2]

In some patients with X-linked CGD, eosinophils, but not neutrophils, retain expression of gp91-*phox*, the largest subunit of the NADPH oxidase system that is deficient in patients with X-linked

CGD, allowing for an intact and functioning NADPH oxidase system. Eosinophils may be able to produce gp91-*phox* due to differential regulation of expression of this protein.[4,5] In addition, eosinophil major basic protein has been shown to activate neutrophils by increasing NADPH oxidase activity; perhaps in CGD there is overexpression of eosinophilic major basic protein in response to the deficient NADPH oxidase system. These phenomena may contribute to the pathogenesis of eosinophilic inflammation in CGD.[6] It is important for the clinician to recognize that corticosteroids used for CGD-associated inflammatory conditions can exacerbate any occult infection. There is evidence that antifungal prophylaxis is of benefit to CGD patients in general,[7] and we consider it extremely important in those patients who are receiving corticosteroids for any reason.

Both children reported herein were diagnosed with eosinophilic inflammation before recognition of CGD, which was suspected only after an unusual infection occurred. Case 1 presented first with dysuria and urinary frequency, which led to the diagnosis of eosinophilic cystitis. Eosinophilic cystitis is rare in pediatrics but has been reported in association with CGD. It is usually self-limited, is characterized by intense local eosinophilic infiltration and can be associated with allergies.[8] The cause of the inflammation in most cases is unknown, but it has been speculated to be an allergic reaction to an infectious agent. In the cases associated with CGD, the symptoms tend to be intermittent and could respond to antibiotics.

Case 2 was diagnosed initially with eosinophilic gastroenteritis. Gastrointestinal complications of CGD are well-described and include gastric outlet obstruction, inflammatory bowel disease and rectal abscesses.[9] In 1 series of 7 patients with CGD, colitis was characterized by eosinophilic crypt abscesses, pigmented macrophages and a paucity of neutrophils; 2 patients had granuloma formation.[10] In a comparison of 8 patients with CGD and colitis with 6 patients with ulcerative colitis, CGD patients had a statistically significant paucity of neutrophils. Eosinophil density was equivalent in both groups, but the eosinophils in CGD patients tended to group around crypt abscesses/cryptitis.[11] These pathologic criteria might help distinguish CGD colitis from other forms of colitis.

Both patients had significant urologic disease caused by different mechanisms. In case 1, the vesicoureteral reflux was thought to be a result of inflammation within the bladder and ureter; whereas in case 2, the obstruction was secondary to external compression from retroperitoneal granulomatous disease. Urologic abnormalities are a known complication of CGD. In 1 retrospective study of 60 patients with CGD, 38% were found to have urologic disease, the majority of which were urinary tract infections, elevated creatinine or outlet obstruction from granulomas or strictures, with genitourinary disease occurring more frequently in X-linked than in the autosomal recessive form of CGD (50% versus 27%).[12] In the national registry of CGD patients, urinary outlet obstruction, thought to be secondary to granuloma formation, was reported in 11% of the X-linked CGD patients and in 7% of the patients with autosomal recessive or unknown mutations.[2] The granulomatous lesions in patients with CGD have been found mainly in the ureters or bladder, leading to dysuria, urinary frequency, hematuria, small bladder capacity and vesicoureteral reflux. The etiology of obstructive granuloma formation in CGD is not known. Urine cultures are often negative, as in case 1. Ureteral obstruction in CGD from retroperitoneal lymph node enlargement causing external compression has also been previously reported.[13] Corticosteroids have been used to treat granulomatous urologic obstruction in CGD with success.[12,14]

The diagnosis of CGD was made in both children after presentation with unusual childhood infections. *A. xylosoxidans* is an aerobic, catalase-positive, Gram-negative rod. *A. xylosoxidans* most typically causes bacteremia (often line associated) and pneumonia in immunocompromised patients.[15,16] Only one other case of *A. xylosoxidans*-associated lymphadenitis has been reported; this patient had hyper-IgM syndrome and a central venous catheter through which he contracted recurrent episodes of *A. xylosoxidans* bacteremia associated with generalized lymphadenopathy.[17] Our second patient was diagnosed with CGD after an *Aspergillus* chest wall infection. In the national registry, *Aspergillus* was isolated from patients with pneumonia in 41% of the cases and was found in 5% of patients with subcutaneous abscesses, 3% with liver abscesses, 23% wuth lung abscesses and 58% with brain abscesses.[2]

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SAFETY AND IMMUNOGENICITY OF PALIVIZUMAB (SYNAGIS) ADMINISTERED FOR TWO SEASONS

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Abstract: To evaluate the safety and immunogenicity of palivizumab, 55 children who received palivizumab in the IMpact-RSV trial received 5 monthly doses of 15 mg/kg palivizumab (Synagis) during the subsequent year. The single child with an antipalivizumab titer of >1/40 had no associated serious adverse events and had expected serum palivizumab trough concentrations. Second year palivizumab prophylaxis was safe and well-tolerated.

Key Words: respiratory syncytial virus, monoclonal antibody, Synagis, palivizumab

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Infants and children who were born prematurely or have bronchopulmonary dysplasia (CLD) or congenital heart disease are at high risk for developing serious respiratory syncytial virus (RSV) infection.[1,2] Palivizumab (Synagis), a humanized monoclonal IgG1 antibody to the RSV fusion protein,[3] has proved safe and effective[4–7] and is indicated for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease.

The safety and efficacy of palivizumab were demonstrated in the IMpact-RSV trial,[5] a 1502-patient (1002 palivizumab, 500 placebo), multicenter, randomized, double blind, placebo-controlled study in high risk infants conducted during a single winter season. A small proportion of children in both the placebo (2.8%) and palivizumab (1.2%) groups[5] developed a titer of >1/40 in an assay for antipalivizumab reactivity.[6] In a multicenter, open label follow-up study to IMpact-RSV, we assessed the safety and immunogenicity of palivizumab during a second season of prophylaxis.

METHODS

Children at 6 selected centers who had participated in IMpact-RSV during the 1996–1997 winter season received palivizumab during the following (1997–1998) season. Children who had received palivizumab in the IMpact-RSV trial received palivizumab for a second season (2-season group) and children who had received placebo in the IMpact-RSV trial received palivizumab for the first time (single season group) in this follow-up study. Investigators and parents were blinded as to whether the children in the current study had received palivizumab or placebo in the IMpact-RSV study of the previous year. As in the palivizumab group in the IMpact-RSV trial,[5] children received 15 mg/kg palivizumab by intramuscular injection every 30 days for a total of 5 doses. The dose of palivizumab was calculated based on the child's weight within 1 week before an injection visit and administered to the child in the anterolateral aspect of the thigh muscle. A complete medical history and physical examination were performed on each dosing day and also 30 days after the final (fifth) injection. Adverse events were reported through 30 days after the last injection and were graded by the investigator for severity and potential relationship to study drug.

The development of serum antipalivizumab reactivity (titer >1/40) and safety of palivizumab were analyzed, with particular reference to the relationship between antipalivizumab reactivity and serious adverse events as well as trough serum levels of palivizumab. Serum samples for assessment of palivizumab concentrations and antipalivizumab reactivity were collected before dosing on the first dosing day (study day 0), 30 days after the first injection (study day 30) and 30 days after the fourth injection (study day 120). Serum concentrations of palivizumab and antipalivizumab reactivity were measured by enzyme-linked immunosorbent assays as previously described.[6]

The study was conducted at 6 sites in the United States and was approved by the Institutional Review Board at each site. Written informed consent was obtained from the parent(s) or guardian of all participants.

RESULTS

Of 88 former IMpact-RSV participants, 56 children received palivizumab for a second season (2-season group), and 32 children received palivizumab for the first time (single season group); 87 children received all 5 and 1 child received 2 injections. Baseline demographics and patient characteristics were not different between the 2 groups; the majority of children in each group had a gestational age at birth of ≤32 weeks (89%) and did not have CLD (80%).

No child in either group had an antipalivizumab titer of >1/40 before dosing on study day 0. Only one child (in the 2-season group) had an antipalivizumab titer of >1/40 after the start of dosing; he had a titer of 1/160 on study day 30 that fell to 1/10 by study day 120 (30 days after the fourth injection). Corresponding trough palivizumab serum concentrations in this child were not lower than expected: 66 μg/mL on study day 30; and 96 μg/mL on study day 120. No serious adverse events were temporally associated with the increased antipalivizumab titer in this child. Two children in the current study had had transient antipalivizumab reactivity during the IMpact-RSV trial with peak titers of 1/80 (single season group) and 1/40 (2-season group), respectively. Neither of these children had antipalivizumab reactivity upon entry into the current study or developed reactivity during the study.

Intramuscular injections of palivizumab were well-tolerated in children receiving the drug for either a first or second season. There were no deaths, and no child was discontinued from the study because of adverse events. No local or systemic adverse events suggestive of an immune-mediated response were noted after any injection, and injection site reactions were rare (one child in each group) and mild. Analysis of adverse events showed no significant differences between the groups with the exception of otitis media (34% in the single season group and 71% in the 2-season group, $P = 0.002$) and teething pain (3 and 20%, respectively, $P = 0.049$); none was judged by the investigator to be related to palivizumab. This study of 88 patients had sufficient statistical power to detect only major differences in incidence of adverse events. Adverse events judged to be related to palivizumab were reported in 2 of 32 (6%) single season and 4 of 56 (7%) 2-season group children. These events included the following: mild injection site pain after the first injection in 1 child in each group; mild to moderate elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) on study day 120 in one single season group (ALT = 297 IU/mL) and two 2-season group (AST = 234 IU/mL and ALT = 98 IU/mL, respectively) children; and fever (102.4°F) in one 2-season group child. Repeat evaluations in the 3 children with liver transaminase elevations were normal within 30 days for the 2 children in the 2-season group and 2 months later for the single season group child.

Two children, both in the 2-season group (2 of 56, 4%), were hospitalized for RSV infection during the study, one after the second dose and one after the third dose of palivizumab. Both hospitalizations were brief (1 and 3 days); neither child required mechanical ventilation or intensive care unit admission.

TABLE 1. Trough Serum Palivizumab Concentrations in Children Receiving Palivizumab Prophylaxis for 1 or 2 Years

	Single Season Group (μg/mL)	2-Season Group (μg/mL)
Study day 30*		
N	32	54
Mean (SE)	60.6 (3.5)	60.7 (2.4)
Range	19.5–110.4	33.6–101.3
Study day 120†		
N	32	55
Mean (SE)	89.0 (5.9)	86.2 (4.2)
Range	39.2–158.9	34.2–197.3

*30 days after the first injection.
†30 days after the fourth injection.

Mean trough serum palivizumab concentrations after the first (obtained on study day 30) and fourth (obtained on study day 120) injections were similar between the 2 groups (Table 1) and well above the target concentration of 25–30 μg/mL that is associated with a 2-log reduction of pulmonary RSV concentrations in the cotton rat model.[3]

DISCUSSION

The data from this study support the safety and tolerance of palivizumab prophylaxis through 2 seasons in children with CLD or prematurity. Administration of palivizumab for a second year did not result in a specific antipalivizumab antibody response nor in local or systemic adverse events suggestive of an immune-mediated reaction. No child in the 2-season group had an antipalivizumab titer $>$1/40 in samples collected before dosing in this study, and only 1 had a $>$1/40 elevation in antipalivizumab titer (1/160) which declined on continued dosing. Antipalivizumab reactivity was not observed in the 2 children who had previously developed antipalivizumab reactivity in the IMpact-RSV study. No pattern of clinical events or alterations of expected serum palivizumab concentrations was associated with the appearance of antipalivizumab reactivity.

In studies conducted to date, immune responses to palivizumab have been uncommon. Transient, low titer antipalivizumab reactivity was detected at 7 days in about one-third of adult volunteers after a single or first administration of palivizumab (Investigational New Drug files; MedImmune, Inc., Gaithersburg, MD). These antibodies disappeared by 14–56 days postdosing and were generally not seen with repeat doses of palivizumab. The specificity of this binding was evaluated by enzyme-linked immunosorbent assay with a panel of monoclonal antibodies and human Fc. The pattern of binding suggested specific antiidiotypic antibody to palivizumab. None of these adults experienced adverse events attributable to the antibody, and slopes of palivizumab concentration over time were similar in volunteers with and without antiidiotypic antibody.

In early pediatric studies, low antipalivizumab titers were observed infrequently after administration of palivizumab and appeared in both children who received placebo and those who received palivizumab.[4–6] Unlike reactivity in adult volunteers, characterization of the antipalivizumab binding for all but 1 child in these studies identified a nonspecific reactivity that was not bound by staphylococcal protein A (thus was not IgG) and was directed to the Fc portion of palivizumab and other human IgG antibodies, rather than the variable portion of palivizumab or its murine monoclonal antibody precursor.[6] This pattern was not suggestive of an antibody response following repeated doses of palivizumab.

Our results are similar to those recently reported by Lacaze-Masmonteil et al,[8] who found that no child receiving palivizumab for the first (n = 71) or second (n = 63) season had an antipalivizumab response $\geq$1/80 and that serum palivizumab concentrations and the incidence of serious adverse events were similar between the 2 groups.

In summary, palivizumab was shown to be safe and well-tolerated during the course of 1 or 2 seasons of prophylaxis in children with a history of CLD or prematurity.

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RIFABUTIN-ASSOCIATED UVEITIS IN A CHILD

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Abstract: Uveitis associated with rifabutin treatment is a well-known adverse effect in adults with human immunodeficiency virus infection. In children, however, uveitis related to rifabutin has been reported in only a few cases. We present a case of rifabutin-associated uveitis in a human immunodeficiency virus-negative child. We review the literature and discuss special precautions to be considered when children are treated with rifabutin.

Key Words: rifabutin, uveitis, children
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Rifabutin is a semisynthetic derivative of rifamycin, which is mainly used for treatment of *Mycobacterium avium* complex (MAC) infections. Uveitis related to this treatment is a well-known side effect in adult patients with human immunodeficiency virus (HIV) infection. The MAC study group reported that 23 of 59 (39%) adults with acquired immunodeficiency syndrome (AIDS) developed uveitis during treatment with rifabutin.[1] In children, however, only a few cases of rifabutin-associated uveitis have been reported,[2–6] possibly due to the difficulties of diagnosing uveitis in children, as they do not always complain of visual changes.

We present a case of bilateral rifabutin-associated uveitis in a 7-year-old HIV-negative child with a congenital immunodeficiency disease. The purpose of this case report is to highlight the spectrum of ocular side effects of rifabutin and to discuss the necessity of special precautions when children are treated with this drug.

CASE REPORT

This case concerns an HIV-negative 7-year-old girl with a congenital, autosomal dominant, interferon-γ receptor 1 defect, which causes reduced resistance to mycobacteria. In September 2002, she developed osteomyelitis in the left clavicle. Culture of a biopsy from the left clavicle showed an atypical mycobacterium, and she was treated with rifabutin 300 mg/d (13 mg/kg), myambutol 300 mg/d (13 mg/kg) and clarithromycin 250 mg/d (11 mg/kg) for nearly 1 year.

After 11½ months of treatment, she developed pain, photophobia and redness of the left eye. Visual acuity in the right eye was 20/25. Visual acuity in the left eye was reduced to 20/32. Slit lamp examination showed diffuse fluffy deposits on the posterior surface of the cornea in both eyes. The right eye was pale with a mild anterior uveitis. In the left eye, there was a dense anterior uveitis and vitritis. The optic nerves and retinae appeared normal. No chorioretinal lesions, vasculitis or evidence of prior inflammation were noted. Laboratory testing showed no antibodies for *Borrelia, Toxoplasma* or cytomegalovirus. There were no antinuclear antibodies or rheumatoid factor. Angiotensin-converting enzyme was normal, and the patient was HLA-B27 negative.

The uveitis was considered to be related to rifabutin treatment, and rifabutin, myambutol and clarithromycin were discontinued after a bone scintigraphy showed normal conditions. She was treated with topical steroids initially 6 times a day. The anterior uveitis and the dense vitritis improved 1 week after discontinuation of rifabutin, confirming that the uveitis was related to rifabutin treatment.

Six months later, visual acuity was 20/25 bilaterally. The uveitis and the vitritis had disappeared, but the deposits on the posterior surface of the cornea persisted, explaining the slightly reduced vision of 20/25 in both eyes. There has been no recurrence of uveitis 7 months after discontinuation of rifabutin treatment.

DISCUSSION

Uveitis is a well-recognized side effect of rifabutin therapy, but nearly all reported cases to date have been adult patients with HIV infection. Only 5 cases have been reported in children.[2–6] Of these 5 cases, 3 children were HIV-positive and 1 child was iatrogenically immunosuppressed because of earlier lung transplantation. The fifth patient had osteomyelitis with *M. avium* complex; no further information was given about this patient.

Of the 5 children reported with rifabutin-associated uveitis, 4 presented with symptoms of acute uveitis.[2–5] The symptoms were blurred vision, redness, photophobia and pain. Ophthalmologic examination showed anterior uveitis with or without hypopyon and different degrees of vitritis. The last reported patient[6] was an 8-year-old boy without ocular symptoms. The uveitis was diagnosed at a routine examination because of his medication. He had decreased visual acuity and mild anterior uveitis with deposits on the posterior surface of the cornea and anterior lens surface. Electrophysiologic examination disclosed retinal dysfunction, which was reversible after discontinuation of rifabutin. Our patient had asymptomatically mild anterior uveitis in the right eye and severe symptomatic panuveitis in the left eye.

All children reported with rifabutin-associated uveitis were treated with topical steroids, and rifabutin was discontinued. There was no reported recurrence of uveitis after the rifabutin treatment was stopped. Some of the cases had persistent deposits in the anterior chamber. This was also seen in our patient and is a known potential side effect of rifabutin therapy.[7] In the case described by Ponjavic et al,[6] progressive accumulation of deposits in the anterior chamber were seen almost 2 years after termination of rifabutin treatment.

In adults, the presenting symptoms of rifabutin-associated uveitis have been pain, redness, photophobia and decreased visual acuity. Ophthalmologic examination has shown anterior uveitis with or without hypopyon and different degrees of vitritis. Cystoid macular edema and retinal vasculitis have also been described in adults. In all cases, the ocular manifestations have been reversible after treatment with topical steroids and discontinuation of rifabutin therapy.

Onset of uveitis after commencement of rifabutin therapy ranged from 51 to 300 days with a mean of 136 days in the 5 children reported. In adult AIDS patients, onset of uveitis after commencement of rifabutin treatment ranged from 27 to 197 days with a mean of 65 days.[1] Our patient developed the first symptoms 345 days after start of rifabutin therapy.

It is not known whether the pathogenesis of rifabutin-associated uveitis is direct rifabutin toxicity or related to lysed MAC organisms. Clinical observations are consistent with direct rifabutin toxicity. In a case control study, Shafran et al[8] examined adult AIDS patients treated with rifabutin for MAC infections. Of 8 factors evaluated, only baseline body weight predicted development of uveitis by univariate and multivariate analysis. The lower the body weight, the higher is the incidence of uveitis, suggesting that the serum concentration of rifabutin plays a role in the development of ocular symptoms. Furthermore concomitant use of clarithromycin and rifabutin may predispose to development of uveitis because clarithromycin can elevate serum rifabutin concentration by inhibition of the hepatic microsomal cytochrome P-450 system that metabolizes rifabutin.[9]

According to Micromedex,[10] it is recommended that rifabutin dosage should be 18.5 mg/kg daily for children younger than 1 year of age. In the age group 2–10 years, the recommended dosage is 8.6 mg/kg daily. The 7-year-old girl reported in this case weighed 22.9 kg and was treated with 300 mg of rifabutin daily (13 mg/kg). Because she was treated concurrently with clarithromycin, the serum concentration of rifabutin might have been elevated, predisposing her to the development of uveitis.

In conclusion, this case report highlights the importance of being aware of possible ocular side effects of rifabutin, which can manifest as silent uveitis. Because children might not always notice or complain of visual changes, we recommend that the ocular status of children treated with rifabutin be monitored during treatment as we do with children, who have other diseases associated with silent uveitis (eg, juvenile idiopathic arthritis).[11]

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