# Brief Reports

## RESPIRATORY CORONAVIRUS INFECTIONS IN CHILDREN YOUNGER THAN TWO YEARS OF AGE

The human coronaviruses (HCoV) comprise many antigenic variants, with the two serogroups represented by strains OC43 and 229E being the most common ones. HCoV infections have been associated with common colds in children and adults and with wheezing in young children with recurrent respiratory infections.[1, 2] Reinfections with HCoV are common, and the virus may be carried for extended periods in the upper respiratory tract.[2] Pitkäranta et al[3] recently found HCoV, using the reverse transcriptase polymerase chain reaction (RT-PCR) technique, in 17% of the middle ear fluid (MEF)/nasopharyngeal aspirates (NPA) in children with acute otitis media (AOM). In Finland 40% of children were reported to have antibodies against the strain OC43 by the age of 2 years and practically all of them had antibodies by the age of 6 years.[4, 5] However, no extensive studies to define better the role of HCoV in respiratory infections have been undertaken.

Although HCoV infections are common, routine diagnostic panels for respiratory infections do not usually include a test for HCoV. Specific diagnosis of coronavirus infections has been very cumbersome. Virus isolation in cell culture is difficult, insensitive and time-consuming. Serologic methods (complement fixation, enzyme-linked immunosorbent assay) do not allow rapid virus identification. Virus detection in NPA with an indirect immunofluorescence assay using monoclonal antibodies is considered to be sensitive,[6] but it is not commonly used to detect viruses in clinical specimens.[7] The recently developed RT-PCR enables the detection of HCoV RNA directly from clinical samples with a high level of sensitivity.[3, 6–8]

We have adopted a previously published duplex RT-PCR technique for HCoV strains OC43 and 229E and combined it with microplate hybridization. The purpose of this study was to evaluate the applicability of this technique to the analysis of large numbers of specimens and to determine the presence of HCoV in a set of NPA and MEF specimens collected from infants in association with upper respiratory infection or AOM.

**Patients and methods.** The specimens were derived from the collections of the Finnish Otitis Media (FinOM) Cohort Study carried out in the Hervanta area, in Tampere, Finland, from May, 1994, to June, 1997. After obtaining informed consent from the parents, we enrolled 329 children at the age of 2 months, and the clinical follow-up continued up to 24 months of age. The families were encouraged to take the child to the study clinic whenever he or she was suffering from acute respiratory infection, and especially if AOM was suspected. During these visits NPA was obtained routinely with a Pediatric Mucus Extractor (Orion Diagnostica, Espoo, Finland).

Criteria for the diagnosis of AOM were a visually abnormal tympanic membrane (with regard to color, position and/or mobility) suggesting middle ear effusion, together with at least one of the following symptoms or signs of acute infection: fever, earache, irritability, diarrhea, vomiting, simultaneous respiratory infection or acute otorrhea not caused by otitis externa. In the case of AOM with effusion, MEF specimens were drawn from the inflamed ear(s). The NPA and MEF samples were frozen immediately after collection and stored at −70°C for 1 to 4 years before the analysis. The time-resolved fluoroimmunoassay method[9] was used to detect antigens of adenoviruses, respiratory syncytial virus, parainfluenza virus types 1, 2 and 3 and influenza viruses A and B in the NPA and MEF samples. The samples had been analyzed for human rhinovirus by a previously published, combined isolation-RT-PCR method.[10]

A systematic report on occurrence of these viruses will be prepared separately.

**HCoV RT-PCR and hybridization.** Extraction of viral RNA from NPA and MEF samples was performed with a commercial RNA isolation procedure (RNeasy, Qiagen GmbH, Hilden, Germany). RT-PCR for HCoV RNA was carried out by previously published methods with minor modifications.[8, 10] Pairs of primers complementary to the HCoV nucleocapsid protein gene for both HCoV OC43 and 229E, 50 pmol of each, were used in the same reaction. At the reverse transcription step the virus-specific oligonucleotide primers were 5′-GCAAGAATGGGGAACTGTGG (OC43) and 5′-GACTATCAAACAGCATAGCAGC (229E). In the PCR the 5′-biotinylated forward primers were 5′-AGGAAGGTCTGCTCCTAATTC (OC43) and 5′-GGTACTCCTAAGCCTTCTCG (229E). Reverse transcription was carried out in a final volume of 40 μl including 5 μl of RNA. The mixtures were incubated for 60 min at 37°C and then heated for 10 min at 65°C. PCR was performed in 96-well plates in a final volume of 100 μl with 5 μl of complementary DNA. Forty cycles of PCR were run using published parameters.[8]

The microplate hybridization assay was carried out as previously published for human rhinovirus detection[10] with some minor modifications. Five microliters of the PCR product were allowed to bind to streptavidin-coated microwells (Labsystems, Helsinki, Finland) and, after alkaline denaturation, exposed for 60 min at 36°C to the hybridization probes: 5′-TATTGGGGCTCCTCTTCTG for the HCoV OC43 and 5′-ACAACACCTGCACTTCCAAA for the 229E. Dinitrophenyl coupled to the 5′-end of the probes was detected by the immunoperoxidase reaction.[10]

**Interpretation of results.** Preparations of RD cell cultures infected with HCoV 229E (American Type Culture Collection, Rockville, MD) and OC43 (provided by Kathryn V. Holmes, University of Colorado, Denver, CO) were used as positive controls. At each step several negative controls were included. The results were calculated from the optical density values. The cutoff value of positive samples was defined as the mean of all the negative samples in each plate (altogether 20 samples) plus 5 times the standard deviation of the mean. If the optical density value was less than the mean of the negative controls plus 3 times standard deviation of the mean, the sample was considered to be negative. The samples yielding values between these two thresholds were reassayed by a confirmatory test for the hybridization step.[10] Eighteen samples were reassayed, and one of them was confirmed to be positive. This was also documented by gel electrophoresis. According to comparative tests using serial dilutions of the prototype strains, the sensitivity of the HCoV RT-PCR was of the same range as that of virus isolation in RD cells.

**Results.** Of the 2005 NPA and 1133 MEF specimens collected in the FinOM Cohort study, 1475 (74%) NPA and 391 (35%) MEF specimens were available for the analysis of HCoV RNA. They were derived from 279 children. Thirty-five tested NPA samples (2.4%) were positive for HCoV, 17 for the type OC43 and 19 for the type 229E (Fig. 1). One sample was positive for both OC43 and 229E. Thirteen NPA-positive children had acute otitis media as the main diagnosis at sample collection. A coinciding MEF(s) specimen was available in 4 cases; all 4 were negative for HCoV. HCoV RNA was also detected in 10 MEF specimens (3%); 7 samples were positive for OC43 and 3 for 229E. In all cases a coinciding NPA was analyzed, but they were negative for HCoV. Other viruses were found in 9 of the 35 HCoV-positive NPA specimens; 7 samples were positive for rhinovirus, 1 for respira-

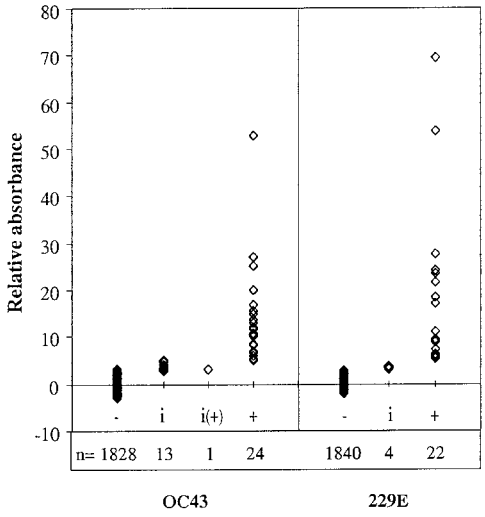


FIG. 1. Absorbances of 1866 nasopharyngeal aspirates and middle ear fluid samples analysed for human coronavirus OC43 and 229E RNA. Original absorbance values have been transformed to relative values. −, negative; *i*, intermediate; *i*(+), intermediate, confirmed to be positive; +, positive sample.

tory syncytial virus and 1 for both rhinovirus and influenza B virus. One HCoV-positive MEF sample was positive for rhinovirus. Rhinovirus was the most commonly detected virus in the analysis of the entire material (S Vesa, M Kleemola, S Blomqvist, A Takala, T Kilpi and T Hovi, manuscript in preparation).

Clinical diagnoses recorded in association with the HCoV-positive NPA are shown in Table 1. The main diagnoses at the time of the HCoV infection were AOM (13) and upper respiratory infection (13). The detected HCoV infections occurred from August to March during the study years. Specimens available did not allow systematic analysis of the length of HCoV infection. Eight of the children had a HCoV-negative MEF before the HCoV-positive MEF specimen (time range, 9 days to 3 months) and 3 of these children also had a negative MEF ~1 month after the detection of HCoV in the MEF samples. In 18 children with HCoV-positive NPA sample, the next NPA was taken; <1 month afterwards (range, 2 to 34 days). Only 1 child had 2 HCoV-positive NPA samples, collected 5 days apart.

**Discussion.** Little is known about HCoV infections in small children, partly because of the difficulties of conventional diagnostic methods. Now RT-PCR has been introduced for epidemiologic studies and also for clinical diagnostic purposes. In the present study we found that HCoV were detectable by RT-PCR in 2.4% of NPA samples of children with acute respiratory infection and/or AOM and in 3% of MEF samples of children with AOM. The 2.4% coronavirus infection rate is lower than in some previous studies with children,[2, 3] possibly because our children were very young. Indeed several serologic studies suggest that the frequency of HCoV infections in children <2 years old is relatively low (antibody prevalence, 3 to 8%), but with older children and during the epidemics, which may occur every 2 to 3 years, the incidence can rise to 19%.[5, 11–13] Hence the apparent paucity of the observed infections may also reflect a specific epidemiologic situation in the population.[4, 5] Variable incidences have also been reported in adults.[1, 14] According to serologic studies almost one-half of the HCoV infections are asymptomatic[11] and therefore could have remained unrecognized in the current study.

In conclusion we have adopted an RT-PCR-hybridization assay for large scale testing of HCoV OC43 and 229E in respiratory specimens. A pilot analysis of stored NPA and MEF specimens revealed a HCoV infection in 2.4% of the specimens, about one-half of them collected in association with AOM. This result justifies the addition of this test to the diagnostic panel of comprehensive respiratory virus detection studies.

**Acknowledgments.** This work was partly supported by Wyeth-Lederle Vaccines and Pediatrics, Merck & Co., Inc. and Pasteur Mérieux Sérums et Vaccins and Helsinki University Central Hospital Research Fund. We thank Virva Jäntti for her advice concerning database searches and Kristiina Aitkoski, Annamari Harberg and Leena Palmunen for their excellent technical assistance.

Johanna Nokso-Koivisto, M.D.
Anne Pitkäranta, M.D.
Soile Blomqvist, M.Sc.
Terhi Kilpi, M.D.
Tapani Hovi, M.D.

Department of Otorhinolaryngology
University of Helsinki (JNK, AP)

Departments of Virology (JNK, SB, TH) and Vaccines (TK)
National Public Health Institute (KTL)

Helsinki, Finland

**TABLE 1.** Clinical diagnosis associated with human coronavirus-positive NPA

| Diagnosis* | No. of Patients | | |
|---|---|---|---|
| | OC43 | 229E | Total |
| Otitis media, acute | 7 | 6 | 13 |
| Upper respiratory infection† | 4 | 9 | 13 |
| Residual effusion after otitis media | 4 | 2 | 6 |
| Bronchitis, acute | 2 | 2 | 4 |
| Exanthema, viral | 1 | 1 | 2 |
| Conjunctivitis, acute | | 2 | 2 |
| Laryngitis, acute | 1 | 1 | 2 |
| Herpangina | | 1 | 1 |
| Tonsillitis, acute | 1 | | 1 |
| Pneumonia | | 1 | 1 |
| Fever | 1 | | 1 |

* In eight patients two or more diagnoses were reported.
† One NPA sample was positive for both OC43 and 229E.

Accepted for publication Oct. 27, 1999.
Key words: Children, human coronavirus, otitis media, respiratory infection.
Reprints not available.

1. Mäkelä MJ, Puhakka T, Ruuskanen O, et al. Viruses and bacteria in the etiology of the common cold. J Clin Microbiol 1998;36:539–42.
2. Isaacs D, Flowers D, Clarke JR, Valman HB, MacNaughton MR. Epidemiology of coronavirus respiratory infections. Arch Dis Child 1983;58:500–3.
3. Pitkäranta A, Virolainen A, Jero J, Arruda E, Hayden FG. Detection of rhinovirus, respiratory syncytial virus, and coronavirus infections in acute otitis media by reverse transcriptase polymerase chain reaction. Pediatrics 1998;102:291–5.
4. Ukkonen P, Hovi T, von Bonsdorff CH, Saikku P, Penttinen K. Age-specific prevalence of complement-fixing antibodies to sixteen viral antigens: a computer analysis of 58 500 patients covering a period of eight years. J Med Virol 1984;13:131–48.
5. Hovi T, Kainulainen H, Ziola B, Salmi A. OC43 strain-related coronavirus antibodies in different age groups. J Med Virol

1979;3:313–20.
6. Sizun J, Arbour N, Talbot PJ. Comparison of immunofluorescence with monoclonal antibodies and RT-PCR for the detection of human coronaviruses 229E and OC43 in cell culture. J Virol Methods 1998;72:145–52.
7. Ieven M, Goossens H. Relevance of nucleic acid amplification techniques for diagnosis of respiratory tract infections in the clinical laboratory. Clin Microbiol Rev 1997;10:242–56.
8. Pitkäranta A, Arruda E, Malmberg H, Hayden FG. Detection of rhinovirus in sinus brushings of patients with acute community-acquired sinusitis by reverse transcription-PCR. J Clin Microbiol 1997;35:1791–3.
9. Räty R, Kleemola M, Melén K, Stenvik M, Julkunen I. Efficacy of PCR and other diagnostic methods for the detection of respiratory adenoviral infections. J Med Virol 1999; 59:66–72.
10. Blomqvist S, Skyttä A, Roivainen M, Hovi T. Rapid detection of human rhinovirus in nasopharyngeal aspirates by microwell reverse transcription-polymerase chain reaction-hybridization assay. J Clin Microbiol 1999;37:2813–6.
11. Kaye HS, Marsh HB, Dowdle WR. Seroepidemiologic survey of coronavirus (strain OC43) related infections in a childrens population. Am J Epidemiol 1971;94:43–9.
12. McIntosh K, Kapikian AZ, Turner HC, Hartley JW, Parrot RH, Chanock RM. Seroepidemiologic studies of coronavirus infection in adults and children. Am J Epidemiol 1070;91: 585–92.
13. McIntosh K, Chao RK, Krause HE, Wasil R, Mocega HE, Mufson MA. Coronavirus infection in acute lower respiratory tract disease of infants. J Infect Dis 1974;130:502–7.
14. Arruda E, Pitkäranta A, Witek TJ Jr, Doyle CA, Hayden FG. Frequency and natural history of rhinovirus infections in adults during autumn. J Clin Microbiol 1997;35:2864–8.

## NEONATAL SEPTICEMIA CAUSED BY *VIBRIO CHOLERAE* O:139

*Vibrio cholerae* serogroups O:1 and O:139 produce clinical cholera. Non-O:1 *Vibrio cholerae* is more invasive and has been known to cause gastroenteritis and extraintestinal manifestations including septicemia.[1] Septicemia with a non-O:1 group has been documented in cirrhotics,[2] in patients with insulin-dependent diabetes mellitus,[3] in a patient with nephrotic syndrome[4] and in a patient with burns.[5] Cholera is uncommon in breast-fed neonates and septicemia in infants with this organism is even rarer. We report a case of *V. cholerae* O:139 septicemia in a 5-day-old neonate.

A single, live female infant was born normally at 37 weeks gestation to a primigravida after a supervised, uneventful antenatal period. The birth weight was 2.4 kg. The baby was mildly asphyxiated with Apgar scores of 7 and 9 at 1 and 5 min, respectively. The baby was kept in the nursery for 50 h and fed expressed breast milk, given in a cup, while breastfeeding was established. No prelacteal feedings were given. During the hospital stay, for a period of 24 h the staff members handling this baby were also managing a woman in the adult ward with *V. cholerae* O:139 gastroenteritis. The baby was readmitted 15 h after discharge with a history of refusal to feed and bluish discoloration of the limbs and face, which developed 6 h after discharge. The baby had had six small, yellowish, semisolid stools since discharge but had not vomited and had been fed expressed breast milk given by a cup.

At the time of admission the neonate was moribund, with marked cyanosis of the limbs and the buccal mucosa. She was severely dehydrated and weighed 1.8 kg. Signs of circulatory collapse were evident. The abdomen was soft and bowel sounds were heard.

A blood culture was obtained on admission and the infant was treated with intravenous cefotaxime, 150 mg/kg/day. The baby died 5 h after admission.

Blood culture was performed by standard techniques.[6] The first subculture (after overnight incubation of the culture) grew a Gram-negative bacillus that was oxidase-positive. It was identified as *V. cholerae* serogroup O:139 by standard biochemical tests[7] and confirmed serologically.

Non-O:1 strains of *V. cholerae* are associated with extraintestinal infections in contrast to the noninvasive enterotoxigenic O:1 strains.[8] Among the reports of non-O:1 *V. cholerae* septicemia, most have been in patients with underlying cirrhosis or with other underlying disease with poor host defense.[2, 3] Relative immunologic immaturity could have played a role in the disease of this 37-week gestational age neonate.

Transmission of infection in *V. cholerae* infections is usually through ingestion of contaminated food. However, nosocomial transmission has been reported in six patients with cirrhosis.[4] The nosocomial nature of this baby's illness is postulated, because illness occurred >48 h after initial admission, with no history of maternal illness.

Anuradha Bose, M.D., D.C.H., M.R.C.P.
John Kenneth Philip, M.B.B.S.
Mary Jesudason, M.D., D.C.P.

Department of Community Health
Christian Medical College (AB)

Department of Clinical Microbiology
Christian Medical College Hospital (JKP, MJ)

Vellore, India

Accepted for publication Oct. 19, 1999.
Key words: *Vibrio cholerae* O:139, septicemia, neonatal.
Reprints not available.

1. Jesudason MV, Lalitha MK, Koshi G. Non O1 *Vibrio cholerae* in intestinal and extra intestinal infections in Vellore, S. India. Indian J Pathol Microbiol 1991;34:26–9.
2. Lin CJ, Chiu CT, Lin DY, Sheen IS, Lien JM. Non-O1 *Vibrio cholerae* bacteremia in patients with cirrhosis: 5-year experience from a single medical center. Am J Gastroenterol 1996; 91:336–40.
3. Fernandez-Natal I, Alcoba-Leza M. Non-O1 *Vibrio cholerae* bacteraemia without diarrhoea. Lancet 1996;348:67.
4. Thomas M, Cherian T, Raghupathy P. Non-O1 *Vibrio cholerae* bacteraemia and peritonitis in a patient with nephrotic syndrome. Pediatr Infect Dis J 1996;15:276–7.
5. Magnusson MR, Pegg SP. *Vibrio cholerae* non-O1 primary septicemia following a large thermal burn. Burns 1996;22: 44–7.
6. Koshi G, Alex W, Menon T. An improved technique for blood culture. Indian J Med Res 1981;73:733–8.
7. Kelly MT, Hickman-Brenner FW, Farmer JJ III. *Vibrio.* In: Balows A, Hansler WJ Jr., Hermann KL, Isenberg HD, Shadomy HJ, eds. Manual of clinical microbiology. 5th ed. Washington, DC: American Society for Microbiology,1991: 384.
8. Morris JG Jr, Black RE. Cholera and other vibrioses in the United States. N Engl J Med 1985;312:343–50.

## MEFLOQUINE-INDUCED PSYCHOSIS

Mefloquine has been used in the treatment of resistant malaria recently and is an effective prophylactic drug. Psychosis as a side effect of mefloquine has been reported in adults,[1, 2] but there have been no reports of this occurring in

children. We report mefloquine-induced psychosis in a 7-year-old Indian child.

**Case report.** A 7-year-old male child was hospitalized for acute onset of fever, vomiting and convulsions and was diagnosed as having cerebral malaria. The illness responded to quinine and was asymptomatic for 1 week when he was readmitted with fever and anemia with a peripheral smear positive for *Plasmodium falciparum*. He was given a repeat course of quinine, but continued to be febrile and anemic with diluted megaloblastic marrow, in spite of repeated blood transfusions. Hence he was grouped as acute severe malaria of R1 resistant type and started on mefloquine therapy. On the 3rd day he had loss of sleep and irrelevant talk; the following day he had hallucinations of insects crawling on the bed and under his garments which worsened in a day, during which period he removed his clothes and started dancing. All these symptoms of psychosis subsided within 24 h of stopping mefloquine.

**Discussion.** Mefloquine, one of the most common antimalarials is a safe therapeutic agent.[1] Some of the reported side effects are seizures, vomiting, nausea, acute psychosis and major disturbances of sleep-wake rhythm.[1, 2] The risk of reactions in adults is 60 times higher in therapeutic users than in prophylactic users.[2] Some authors have reported dizziness, vertigo, skin reactions, paresthesias, unsteadiness, unconsciousness, anxiety, depression and psychosis.[3] Most of the references retrieved from a MEDLINE search showed reported cases of mefloquine psychosis in adult patients[2, 4, 5] and none in the pediatric age group. Whether the incidence of side effects in children is more or less than in adults is not clear. Hence an alternate regimen of a single dose of 12.5 mg of mefloquine per kg combined with sulfadoxine and pyrimethamine than the total of 25 mg of mefloquine per kg in 2 to 3 divided doses has been recommended.[2]

Mefloquine does interfere with the pharmacokinetics of antiepileptic drugs like sodium valproate, and dosage modifications have been advised.[6] More reports on the side effects of mefloquine in children from the malaria-endemic countries may help in evolving consensus guidelines for use in children.

Parvat V. Havaldar, M.D., D.C.H., D.T.M.H.
Kavitha D. Mogale, M.D.
Department of Pediatrics
KLES Hospital and Medical Research Centre
Belgaum, India

Accepted for publication Oct. 27, 1999.
Key words: Mefloquine, psychosis, malaria.
Address for reprints: Dr. P. V. Havaldar, A-5, Staff quarters, J. N. Medical College, Belgaum 590010, India. Fax 0091-831-470743; E-mail: blgjnmc@kar.nic.in.

1. Held T, Trautman M, Weinke T, Mravak S. Clinical experiences with mefloquine in tropical malaria: II a prospective study. Immune-Infek 1991;19:83–6.
2. Weinke T, Trautman M, Held T, et al. Neuropsychiatric side effects after the use of mefloquine. Am J Trop Med Hyg 1991;45:86–91.
3. Sturchler D, Handschin J, Kaiser D, et al. Neuropsychiatric side effects of mefloquine. N Engl J Med 1990;1752–3.
4. Burgmann H, Winker S, Uhl F, et al. Mefloquine and sulfadoxine/pyrimethamine overdose in malaria tropica. Wien Klin Wochenschr 1993;105:61–3.
5. Folkerts H, Kuhs H. Psychotic episode caused by prevention of malaria with mefloquine: a case report. Nervenarzt 1992; 63:300–2.
6. Jallon P. Use of mefloquine in epileptic patients. J Neurol Neuro Surg Psychiatry 1988;51:732.

## DONOVANOSIS CAUSING CERVICAL LYMPHADENOPATHY IN A FIVE-MONTH-OLD BOY

Donovanosis, or granuloma inguinale, is endemic in many parts of the developing world, in particular southern Africa, India, the Caribbean, South America, Papua New Guinea and northern Australia.[1] The major clinical manifestations are of genitoulcerative disease, but extragenital disease occurs in ~6% of cases,[1] and there is usually a considerable delay in the diagnosis of such presentations. Donovanosis is predominantly sexually transmitted and is rare in infants. We present a case of presumed vertical transmission in a 5-month-old child which illustrates new approaches to the diagnosis and treatment of the condition.

**Case report.** A 5-month-old Aboriginal boy from a remote community in the Northern Territory of Australia was admitted to hospital for investigation of left-sided cervical lymphadenopathy which had been present for 1 month. He had been treated with oral amoxicillin 1 month previously for an initially bloody, purulent discharge from the left ear. On admission a fluctuant preauricular lymph node and several firm, nontender enlarged cervical nodes at the angle of the left mandible were noted. He also had chronic, suppurative, left otitis media, widespread scabies and mild conjunctival injection consistent with a viral conjunctivitis.

Investigations revealed the following: hemoglobin 80 g/l, mean corpuscular volume 52 fl, platelets $300 \times 10^9$/l and white blood cells $22.8 \times 10^9$/l, including granulocytes 22.8%, lymphocytes 55.7%, monocytes 12.2%, eosinophil 3.9% and basophils 5.3%; C-reactive protein was 37 mg/l (normal, 0 to 8). The blood smear appearance was suggestive of iron deficiency with infection. Mantoux and nontuberculous mycobacterial skin tests (*Mycobacterium avium*) were nonreactive, and melioidosis serology was negative. He was treated in the hospital with intravenous ampicillin and flucloxacillin, dexamethasone-framycetin-gramicidin ear drops and topical permethrin cream. The lymphadenopathy seemed to be improving after 1 week of treatment, and he was discharged receiving oral amoxicillin/clavulanate and given an intramuscular injection of iron.

He was readmitted 2 months later with persisting left cervical lymphadenopathy and gastroenteritis. No stool pathogens were identified and *Strongyloides* serology was negative. His weight was 5.4 kg (weight/age − *Z* score, 3.04), length 63 cm (length/age − *Z* score, 2.43), head circumference 40.7 cm (<2nd centile) and weight-for-height − *Z* score 1.64. He was still fully breast-fed and receiving minimal solid foods in spite of his age. The left cervical lymphadenopathy was nonfluctuant and involved the preauricular, submandibular and cervical glands. Ultrasound examination demonstrated multiple discreetly enlarged glands up to a maximum diameter of 1.7 cm. He also had persisting purulent discharge from his left ear with a "polyp" in his left ear canal with a soft mass of red granulomatous tissue over the tympanic membrane. There was no clinical evidence of mastoiditis. He had temperatures spikes up to 38.5°C which improved on treatment with ampicillin and flucloxacillin. A urine catheter specimen had a pure growth of $10^8$ colonies of *Escherichia coli*, susceptible to ampicillin. Renal ultrasound and micturating cystourethrogram were normal. Chest roentgenogram revealed bronchial wall thickening with no consolidation. Admission hemoglobin was 10.1 g/l with mean corpuscular volume 59.9 fl, platelets $408 \times 10^9$/l, white blood cells $15.3 \times 10^9$/l with red blood cell morphology consistent with response of iron deficiency anemia to treatment. C-reactive protein was 45 mg/l, which fell to <5 mg/l after 2 weeks. HIV-1 and HIV-2 antibodies were not detected.

On this admission it was noted that his 16-year-old mother

had extensive untreated genital donovanosis, which was confirmed by histology of a vulval smear. In light of the slow resolution of the cervical lymphadenopathy and the new clinical information, the child underwent an excision biopsy of a cervical gland. Histology of the lymph node showed chronic fibrosing lymphadenitis with periadenitis and granulation tissue formation. Although pathognomonic Donovan bodies were not seen on the original histologic examination, the detection of *Calymmatobacterium granulomatis* on an in-house PCR assay prompted a review of the slides. Prolonged and meticulous searching of sections stained overnight with Giemsa demonstrated typical Donovan bodies within cytoplasmic vacuoles (Fig. 1). No acid-fast bacilli were seen, and cultures for *Mycobacterium tuberculosis* were negative.

During treatment with oral azithromycin suspension, 10 mg/kg daily for 14 days, the cervical lymphadenopathy resolved. He was readmitted 2 months later with a right middle lobe pneumonia and an *E. coli* urinary tract infection but with no evidence of persisting lymphadenopathy. There was "shotty" axillary lymphadenopathy and 2 cm of spleen palpable. The polyp in the left ear canal had resolved and there was no discharge, although there was a small central drum perforation. The pneumonia and urinary tract infection responded rapidly to intravenous ampicillin and oral nitrofurantoin.

**Discussion.** There are few cases of perinatal transmission of donovanosis documented but the apparent predilection for otic structures is noteworthy. A 5-month-old boy, born to a mother with untreated cervical donovanosis, developed a purulent discharge from the ear with a tympanic perforation and postauricular swelling. The child subsequently developed lesions involving the umbilicus and penis and a bony lesion in the right radius.[2] Donovanosis has also been reported in the umbilicus of a 6 week old infant[3] and on the labia of a 6-month-old infant.[4] Recently two cases of donovanosis occurring in two HIV-negative South African children (8 months and 5 months of age) causing mastoiditis and external ear discharges were reported.[5] A temporal lobe abscess developed in the 8-month-old child, and the other child had a polypoid mass in the middle ear that on biopsy showed the features of donovanosis. The child's mother was also found to have uterine cervical donovanosis on biopsy.

The diagnosis was not considered in our patient until other important causes of cervical lymphadenopathy had been excluded and donovanosis was detected by chance in the mother. The polyp in the left external auditory canal may have been a donovanosis granuloma, but it was not examined. Histologic examination of tissue smears or biopsies remains the cheapest and most readily available diagnostic method,[1] but the sensitivity is dependent on the skill, experience and perseverance of the pathologist. Culture has been reestablished in South Africa[6] and in our laboratory, but the technique is relatively difficult and relies on the maintenance of viable organisms after specimen collection, something that is extremely difficult outside of hospital and clinic settings. We have developed a PCR for *C. granulomatis* that appears to be more sensitive than histology and has the major advantage of being performable on samples that do not contain live organisms.[7]

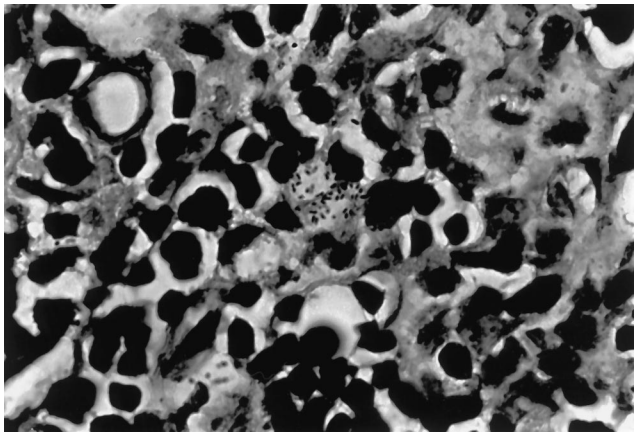

FIG. 1. Donovan bodies in rare mononuclear cells among the chronic inflammatory cell infiltrate in chronic lymphadenitis. Overnight Giemsa, × 2000.

Little attention has been paid in the past to the histology of lymphadenitis caused by donovanosis. Donovan bodies are usually found easily within mononuclear cells when there is acute inflammation,[8] but in this case the lymph node showed chronic inflammation with fibrosis and granulation tissue formation.

*C. granulomatis* is susceptible to a wide array of antibiotics that have Gram-negative activity.[1] Ampicillin has limited efficacy in the treatment of donovanosis, but its use may explain the paucity of Donovan bodies in the excised lymph node. Until recently successful treatment of donovanosis has depended on ensuring compliance with prolonged multiple daily doses of antibiotics. We now have experience with the use of azithromycin for the treatment of donovanosis in adults[9, 10] which allows for a much shorter, intensive course of therapy or once a week dosing. This is the first infant who has been treated with azithromycin in our center. The medication was well-tolerated and led to rapid resolution of the lymphadenopathy. The optimal dosage and duration of therapy have not been established. In adults we use either a 500-mg oral daily dose for 7 days or a 1.0-g weekly dose for 4 weeks with a near 100% cure rate. A shorter course of a larger oral dose of azithromycin (20 mg/kg) may also be effective in children and could be useful in nonhospitalized patients. Children born to mothers with untreated donovanosis should receive antibiotic prophylaxis; the ideal regimen is unknown, but we recommend a 3-day course of once daily azithromycin (20 mg/kg).

It has been our experience that despite the considerable discomfort, characteristic odor and pain associated with this condition, many adult patients, for complex sociocultural reasons, are reluctant to present for treatment. The disease is often diagnosed in the course of other medical procedures, e.g. Papanicolaou smear, antenatal checkup or intrapartum. Clinicians working in endemic areas should therefore pursue a present or past history of donovanosis in the mother that could aid in the diagnosis in the child.

Francis J. Bowden, M.B.B.S., F.R.A.C.P., F.A.C.S.H.P.
April Bright
Jurgen W. Rode, M.B.B.S., D.C.P., M.D., F.R.C.Path., F.R.C.P.A.
David Brewster, B.A.(Hons), M.D., M.P.H., F.R.A.C.P., Ph.D.

AIDS-STD Unit
Territory Health Service
Darwin (FJB)

Northern Territory Clinical School (AB)
Darwin

Anatomical Pathology
Royal Darwin Hospital (JWR)
Darwin

Northern Territory Clinical School
Flinders University (DB)
Adelaide

Australia

Accepted for publication Oct. 27, 1999.
Key words: Donovanosis, granuloma inguinale, lymphadenopathy, azithromycin.
Reprints not available.

1. Richens J. The diagnosis and treatment of donovanosis (granuloma inguinale). Genitourin Med 1991;67:441–52.
2. Scott CW, Harper D, Jason RS, Helwig EB. Neonatal granuloma venereum. Am J Dis Child 1952;85:308–15.
3. Arnell RE, Potekin JS. Granuloma inguinale (granuloma venereum) of the cervix: an analysis of thirty-eight cases. Am J Obstet Gynecol 1940;39:626–35.
4. Banerjee K. Donovanosis in a child of six months. J Indian Med Assoc 1972;59:293.
5. Govender D, Naidoo K, Chetty R. Granuloma inguinale (donovanosis): an unusual cause of otitis media and mastoiditis in children. Am J Clin Pathol 1997;108:510–4.
6. Kharsany AB, Hoosen AA, Kiepiela P, Naicker T, Sturm AW. Growth and cultural characterisitics of *Calymmatobacterium granulomatis*: the aetiological agent of granuloma inguinale (donovanosis). J Med Microbiol 1997;46:579–85.
7. Carter J, Bowden FJ, Sriprakash KS, Bastian I, Kemp DJ. Diagnostic polymerase chain reaction for donovanosis. Clin Infect Dis 1999;28:1168–9.
8. Frienkel AL. Granuloma inguinale of cervical lymph nodes simulating tuberculous lymphadenitis: two case reports and review of published reports. Genitourin Med 1988;64:339–43.
9. Bowden FJ, Mein J, Plunkett C, Bastian I. Pilot study of azithromycin in the treatment of genital donovanosis. Genitourin Med 1996;72:17–9.
10. Skov SJ, Tait P, Kaldor J, Bowden FJ. A field trial of azithromycin in the treatment of donovanosis: a step towards eradication? Venereology 1997;11:11–14.

## HERPES ZOSTER IN HEALTHY CHILDREN IMMUNIZED WITH VARICELLA VACCINE

Herpes zoster rarely develops in healthy children who received varicella vaccine. The incidence of zoster among them was reported to be 14 cases per 100 000 person years.[1] Furthermore zoster in children immunized with varicella vaccine has not always been caused by the varicella Oka vaccine strain.[1] We present two cases of pediatric herpes zoster that developed 3 to 7 years after vaccination against varicella in which causative viruses were revealed by PCR analysis to be wild strains of varicella-zoster virus (VZV).

**Case reports.** *Case 1.* A healthy 1-year-old girl received varicella vaccine (Lot BVZ0034, $2.0 \times 10^4$ plaque-forming units/dose; Biken, Osaka, Japan) on November 27, 1993. On February 25, 1997, at 4 years of age, she developed an exanthema on the left side of her neck which extended to the anterior part of her left ear on the next day. She consulted a dermatologist and was diagnosed as having herpes zoster on February 28. On March 3 her mouth was noted to be abnormally distorted when she sang a song. Because she complained of a strange sensation in her left ear, she visited our hospital. Redness and vesicles were seen in the skin distribution of the third trigeminal branch and the second and third cervical nerve regions. No vesicle was found in the left external auditory canal. The left corner of her mouth drooped and the left nasolabial sulcus disappeared (Ramsay-Hunt syndrome). Lagophthalmus, however, was not observed. She received acyclovir intravenously. On March 4 she could not easily chew her food and complained of slight taste abnormality. She was treated with prednisolone (15 mg/day). All vesicles in the zoster lesions formed crusts on March 10 (14th day of the disease). Her facial palsy gradually improved and she recovered without hearing disturbance. Attempted virus isolation from vesicles in the zoster lesion was unsuccessful, and crusts were collected from zoster lesion to extract VZV DNA.

*Case 2.* A healthy 2-year-old boy received varicella vaccine (Lot BVZ018, $1.8 \times 10^4$ plaque-forming units/dose; Biken) on July 3, 1990. On December 4 he contracted mild varicella with 7 to 8 vesicles in total and without fever. On September 15, 1997 (at 9 years of age), redness and exanthema appeared in the right side of his back and right upper abdomen (T9 to 10 dermatomes). On September 22 he was diagnosed as having herpes zoster by a dermatologist. Because the boy complained of nausea and headache, he was admitted to our hospital and received acyclovir intravenously (750 mg/day). No meningeal sign was present. Zoster lesions began to crust on September 24 and healed uneventfully. Virus isolation was not performed, but crusts were collected to analyze VZV DNA.

**Virologic examinations.** To know whether genomic DNAs extracted from crusts formed in the zoster lesions of the

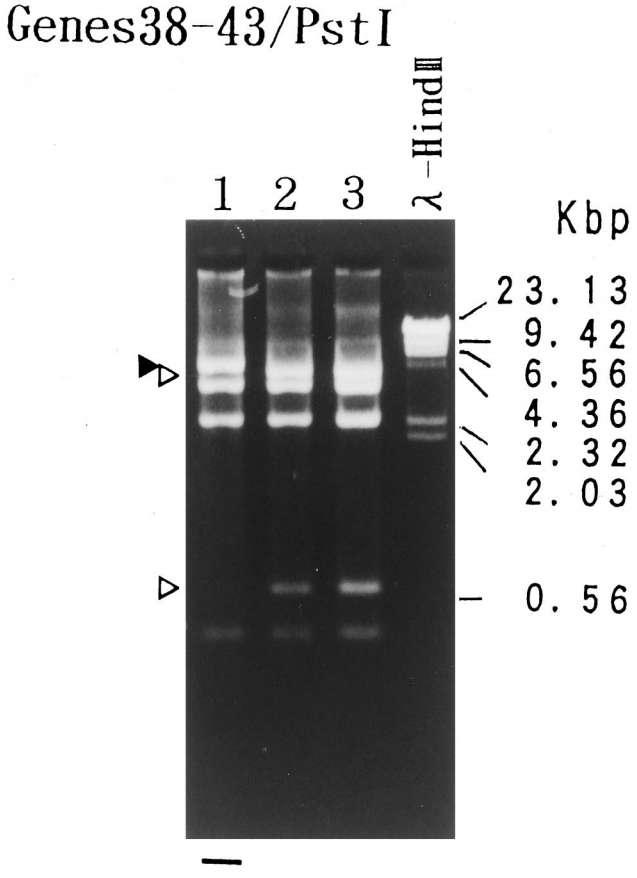


FIG. 1. Restriction fragment length polymorphism analysis of the gene 38 to 43 region digested with *Pst*I. *Lane 1,* DNA from Oka vaccine strain; *Lanes 2* and *3,* DNAs from crust of Cases 1 and 2, respectively. The digests were analyzed in a 1.4% agarose gel. The restriction enzyme site that separates the band indicated with a *closed arrowhead* into the two bands indicated with *two open arrowheads* was absent from the Oka vaccine strain marked with a minus sign at the bottom (*Lane 1*). DNAs from two patients contained the *Pst*I site (*Lanes 2* and *3*).

patients were identical with the DNA of the Oka vaccine strain, we determined whether the DNA contained the *Pst*I restriction site in gene 38 or not. The gene 38 to 43 region was amplified by PCR, and amplification products were analyzed by restriction fragment length polymorphism analysis described previously.[2] The PCR products were precipitated in ethanol and digested with *Pst*I for 2 h at 37°C. The digested PCR products were separated by 1.4% agarose gel electrophoresis and was visualized by ethidium bromide staining.

**Results.** Lack of the *Pst*I restriction site in gene 38 has been identified as a marker for grouping VZV isolates.[2–4] The Oka vaccine strain lacks the *Pst*I site. The cleavage patterns of DNAs obtained from Cases 1 and 2 were identical (Fig. 1) and different from that of the varicella Oka vaccine strain. Both DNAs conserved the *Pst*I site. The results showed that the VZV strains causing zoster in both cases conformed to wild strains.

**Discussion.** Most young zoster patients contracted varicella in early infancy.[5] Some children having zoster with no history of clinical varicella were thought to have been infected with VZV *in utero*.[6] On the other hand in Japan about 20% of children who received varicella vaccine contracted natural varicella 2 to 3 years after immunization (breakthrough varicella).[7] The cause of herpes zoster in Case 1 may be explained by the assumption that she had mild, unrecognized infection with a VZV wild strain in her first year of life or that she was inapparently infected with VZV wild strain after varicella vaccination, like the adult case that Hammershlag et al.[8] reported. The latter seems to be a more likely explanation in Case 1 than the former, because her mother did not have varicella during pregnancy and her brothers did not contract varicella during her first year of life.

The zoster lesion of Case 2 was thought to be produced by the VZV wild strain which caused mild breakthrough varicella after vaccination and remained silently in nerve ganglions thereafter.

If analysis of viral DNA had not been performed, Case 1 would have been mistakenly accepted as a zoster patient affected by the varicella vaccine strain, because her parents denied exposure to varicella. Plotkin et al.[9] reported two cases of herpes zoster in otherwise healthy children after vaccination against varicella. However, they did not perform analysis of VZV DNA; therefore the zoster in these children could have been caused by VZV wild strain. In follow-up studies of children immunized with varicella vaccine, viral DNA analysis should be performed before zoster lesions in vaccinees is attributed to the vaccine strain.

Naohide Takayama, M.D.
Michiko Takayama, Ph.D.
Junko Takita, M.D.
Department of Pediatrics
Tokyo Metropolitan Komagome Hospital
Department of Virology I
National Institute of Infectious Diseases
Tokyo, Japan

Accepted for publication Oct. 27, 1999.
Key words: Herpes zoster, varicella vaccine, varicella-zoster virus, wild strain.

Address for reprints: Naohide Takayama, M.D., Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. Fax 81-3-3824-1552; E-mail takyamndk@komagome-hospital.bunkyo.tokyo.jp.

1. Takahashi M, Gershon AA. Varicella vaccine. In: Plotkin SA, Mortimer EA, eds. Vaccines. 2nd ed. Philadelphia: Saunders, 1994:389–417.
2. Takayama M, Takayama N, Inoue N, Kameoka Y. Application of long PCR method to identification of variations in nucleotide sequences among varicella-zoster virus isolates. J Clin Microbiol 1996;34:2869–74.
3. Hondo R, Yogo Y, Yoshida M, Fujima A, Itoh S. Distribution of varicella-zoster virus strains carrying a *Pst*I-site-less mutation in Japan and DNA change responsible for the mutation. Jpn J Exp Med 1989;59:233–7.
4. LaRussa P, Lungu O, Hardy I, Gershon A, Steinberg S, Silverstein S. Restriction fragment length polymorphism of polymerase chain reaction products from vaccine and wild-type varicella-zoster virus isolates. J Virol 1992;66:1016–20.
5. Terada K, Kawano S, Yoshihiro K, Yokobayashi A, Miyashima H, Morita T. Characteristics of herpes zoster in otherwise normal children. Pediatr Infect Dis J 1993;12: 960–1.
6. Brunell PA, Kotchmar GS. Zoster in infancy: failure to maintain virus latency following intrauterine infection. J Pediatr 1981;98:71–3.
7. Takayama N, Minamitani M, Takayama M. High incidence of breakthrough varicella observed in healthy Japanese children immunized with live attenuated varicella vaccine (Oka strain). Acta Pediatr Jpn 1997;39:663–8.
8. Hammerschlag MR, Gershon AA, Steinberg SP, Gelb LD. Herpes zoster in an adult recipient of live attenuated varicella vaccine. J Pediatr 1989;160:535–7.
9. Plotkin SA, Starr SE, Conner K, Morton D. Zoster in normal children after varicella vaccination. J Infect Dis 1989;159: 1000–1.

## SEVERE EHRLICHIOSIS IN AN ADOLESCENT TAKING TRIMETHOPRIM-SULFAMETHOXAZOLE

Human ehrlichiosis is a tick-borne illness most commonly seen in children with symptoms of fever, headache and malaise associated with leukopenia, thrombocytopenia and increased hepatic enzyme values.[1] A nonspecific rash, seen in one-third of infected adults,[2,3] may occur in up to two-thirds of children with *Ehrlichia*.[1] The proteobacteria *Ehrlichia chaffeensis,* which causes human monocytic ehrlichiosis (HME) is in the family Rickettsiaceae with *Rickettsia rickettsii*, the cause of Rocky Mountain spotted fever, and *Rickettsia conorii*, the cause of Mediterranean spotted fever. It has been reported that sulfonamide drugs increase the severity of both Rocky Mountain spotted fever and Mediterranean spotted fever,[4–6] although such observations have not been reported with ehrlichiosis. We present a case of HME that progressed to respiratory failure in an adolescent taking trimethoprim-sulfamethoxazole.

**Case report.** A previously healthy 16-year-old boy living in rural Tennessee developed symptoms of headache, myalgias, migratory arthralgias and fatigue over several weeks beginning in early August. He had been taking oral trimethoprim-sulfamethoxazole (160 mg of trimethoprim and 800 mg of sulfamethoxazole twice a day) for treatment of acne. His symptoms progressed and included fevers, associated rigors and nausea with occasional emesis. On August 20 he was diagnosed with a sinus infection and prescribed ibuprofen, promethazine and diphenhydramine to supplement his antibiotic regimen. However, his symptoms worsened and the following day he refused all medications. On August 25 he developed fever to 104°F, chest pain, bilateral conjunctivitis and a petechial rash on his hands, arms and chest. Two days later he was admitted to a community hospital.

His past history revealed that 2 years previously he had been treated with iv antibiotics for periorbital cellulitis of his left eye with resolution. He removed a tick from his scalp in mid-July after working outside. His household included a

healthy cat and dog, and the patient had no other animal exposures. He had not traveled outside of the United States and had no known exposure to sick persons. His immunizations were up to date.

On admission to the hospital the patient was ill-appearing with a temperature of 104.2°F, pulse 126/min and respirations of 20/min. The blood pressure was 131/63 mm Hg. Physical examination revealed bilateral bulbar and palpebral conjunctivitis without discharge, a fine petechial rash on the hands, arms and feet and diffuse abdominal tenderness. The patient had no respiratory distress, hepatosplenomegaly or nuchal rigidity. Laboratory studies on the day of admission were notable for a serum sodium of 128 mEq/l, a total leukocyte count of 1600 cells/$\mu$l (43% segmented, 20% band forms, 23% lymphocytes, 10% monocytes and 4% atypical lymphocytes), a platelet count of 58 000 cells/$\mu$l and a hematocrit of 38%. Liver enzyme analysis at admission showed an alanine aminotransferase of 157 units/l and an aspartate aminotransferase of 211 units/l. Bacterial cultures of blood and urine sent at that time ultimately showed no growth.

The day after admission consultation with the hematology and infectious diseases services was obtained and the patient was started on intravenous ceftriaxone and vancomycin as empiric coverage for bacterial sepsis as well as intravenous doxycycline for suspected rickettsial disease. Additional laboratory work-up included a partial thromboplastin time of 66.9 s with a prothrombin time within normal range. There were no morulae or other organisms detected on review of the peripheral blood smear. Throughout the day the patient developed worsening respiratory distress and high fever with visual hallucinations. A chest radiograph obtained that morning revealed "a very subtle infiltrate in the right lung base." Later that day the patient's respiratory status deteriorated, necessitating intubation and mechanical ventilation. He was then transferred to the pediatric intensive care unit at Vanderbilt University Medical Center.

Chest radiographs at the time of transfer revealed diffuse interstitial infiltrates throughout both lungs consistent with interstitial pulmonary edema. Subsequent chest radiographs revealed bilateral lower lobe pneumonia with a right sided parapneumonic effusion. The patient required mechanical support of ventilation until the fourth day of his hospitalization when improvement in his respiratory status allowed extubation. *E. chaffeensis* 16S ribosomal DNA was detected by polymerase chain reaction (methods described previously),[7] and the organism was isolated in tissue culture from a peripheral blood sample obtained on admission to Vanderbilt University Medical Center. The patient's fever resolved on the sixth day of hospitalization and laboratory studies revealed complete correction of his hyponatremia, leukopenia, thrombocytopenia and coagulation studies. At the time of discharge on the tenth day of hospitalization, his respiratory function had returned to normal and his symptoms of fatigue, abdominal pain, myalgias, arthralgias and headache had greatly improved. He was discharged on oral doxycycline to complete a fourteen-day course.

**Discussion.** The symptoms of fever, headache, myalgias, anorexia and nausea manifested by our patient are nonspecific findings that are typical of human ehrlichiosis. Rash and conjunctivitis are signs frequently reported as manifestations of ehrlichiosis in children.[1] Residence in a rural area and recent tick attachment are commonly associated with *Ehrlichia* infection as well. The laboratory profile of lymphopenia, thrombocytopenia, elevated aminotransferase levels and hyponatremia is characteristic of this disease.[1] Despite the typical features of this boy's illness, ehrlichial infection is not commonly considered in the evaluation of respiratory failure.

Ehrlichiosis has been reported as a cause of acute respiratory distress syndrome (ARDS)[8,9] and uncommonly may result in a rapidly fatal illness characterized by lung injury and multiple organ failure despite appropriate antibiotic therapy.[10] Of 61 patients with fever and ARDS in New York, 11% had serologic evidence of past infections with *E. chaffeensis* or *Ehrlichia equi* or both.[11] The mechanism of lung injury is unknown, but increased pulmonary vascular permeability mediated by vasodilatory cytokines released from infected cells has been postulated as a cause of ARDS in HME.[9] It is important to consider ehrlichiosis in patients with rapidly progressing respiratory distress and chest radiograph findings of fine reticular granularity of the lung fields typical of ARDS. Pulmonary infiltrates were seen in 75% of children with ehrlichiosis in one report.[2] The rapid progression from a normal chest radiograph to one showing alveolar opacities with pleural effusion, as was seen on our patient, has also been reported in children with ehrlichiosis.[12]

There have been rare reports of an association between sulfonamide antibiotics and increased severity of rickettsial infections in human patients.[4,5] More recently trimethoprim-sulfamethoxazole was shown to be ineffective in treating Mediterranean spotted fever, with findings suggesting that this medication increased the severity of illness in patients studied.[6] Although sulfonamide use has not been shown to increase the pathogenicity of *Ehrlichia* species, a case of HME complicated by ARDS has been reported in a patient who had been treated with oral trimethoprim-sulfamethoxazole.[8] It is interesting to speculate that administration of trimethoprim-sulfamethoxazole may have contributed to the unusual severity of ehrlichiosis in our patient. The mechanism by which rickettsial illnesses may be potentiated by sulfonamide antibiotics is not known. Fulminant rickettsial disease has also been observed in patients with glucose-6-phosphate dehydrogenase deficiency,[13–15] in whom sulfonamide administration can trigger severe hemolysis.[16] Although this is not a likely etiology in our Caucasian patient, this observation may be important in an evaluation of the independent impact of sulfonamides on rickettsial pathogenesis. Also important in the consideration of this case is that a delay in the treatment of HME until 8 days or more after the onset of illness has been statistically associated with an increased risk for complications or death.[3] This patient's illness illustrates the importance of considering rickettsial disease as a cause of fever with headache, myalgias and nausea in children exposed to ticks.

Timothy R. Peters, M.D.
Kathryn M. Edwards, M.D.
Steven M. Standaert, M.D.

Division of Infectious Diseases (TRP, KME)
Department of Pediatrics

Division of Infectious Diseases (SMS)
Department of Medicine

Vanderbilt University Medical Center
Nashville, TN

Accepted for publication Oct. 25, 1999.
Key words: Human monocytic ehrlichiosis, trimethoprim-sulfamethoxazole, *Ehrlichia chaffeensis.*

Address for reprints: Kathryn M. Edwards, M.D., Vanderbilt University Medical Center, Division of Pediatric Infectious Diseases, D-7235 Medical Center North, Nashville, TN 37232-2581.

1. Jacobs RF, Schutze GE. Ehrlichiosis in children. J Pediatr 1997;131:184–92.
2. Eng TR, Harkess JR, Fishbein DB, et al. Epidemiologic, clinical, and laboratory findings of human ehrlichiosis in the United States, 1988. JAMA 1990;264:2251–8.

3. Fishbein D, Dawson J, Robinson LE. Human ehrlichiosis in the United States, 1985 to 1990. Ann Intern Med 1994;120: 736–43.
4. Harrell GT. Treatment of Rocky Mountain spotted fever with antibiotics. Ann NY Acad Sci 1952;55:1027–42.
5. Steigman AJ. Rocky Mountain spotted fever and the avoidance of sulfonamides. J Pediatr 1977;91:163–4.
6. Ruiz Beltran R, Herrero Herrero JI. Deleterious effect of trimethoprim-sulfamethoxazole in Mediterranean spotted fever. Antimicrob Agents Chemother 1992;36:1342–3.
7. Standaert SM, Dawson JE, Schaffner W, et al. Ehrlichiosis in a golf-oriented retirement community. N Engl J Med 1995; 333:420–5.
8. Patel RG, Byrd MA. Near fatal acute respiratory distress syndrome in a patient with human ehrlichiosis. South Med J 1999;92:333–5.
9. Weaver RAR, Virella G, Weaver A. Ehrlichiosis with severe pulmonary manifestations despite early treatment. South Med J 1999;92:336–9.
10. Martin GS, Christman BW, Standaert SM. Rapidly fatal infection with *Ehrlichia chaffeensis*. N Engl J Med 1999;341: 763–4.
11. Wong S, Grady LJ. *Ehrlichia* infection as a cause of severe respiratory distress. N Engl J Med 1996;334:273.
12. Fordham LA, Chung CJ, Specter BB, et al. Ehrlichiosis: findings on chest radiographs in three pediatric patients. AJR 1998;171:1421–4.
13. Walker DH, Radisch DL, Kirkman HN. Haemolysis with rickettsiosis and glucose-6-phosphate dehydrogenase deficiency. Lancet 1983;2: 217.
14. Walker DH, Hawkins HK, Hudson P. Fulminant Rocky Mountain spotted fever: its pathologic characteristics associated with glucose-6-phosphate dehydrogenase deficiency. Arch Pathol Lab Med 1983;107:121–5.
15. Raoult D, Lena D, Perrimont H, et al. Haemolysis with Mediterranean spotted fever and glucose-6-phosphate dehydrogenase deficiency. Trans R Soc Trop Med Hyg 1986;80: 961–2.
16. Glader BE, Lukens JN. Glucose-6-phosphate dehydrogenase deficiency. In: Lee GR, ed. Wintrobe's clinical hematology. 10th ed. Baltimore: Lippincott Williams & Wilkins, 1999: 1177–84.

## SEVERE RHABDOMYOLYSIS, HYPERTHERMIA AND SHOCK AFTER AMPHOTERICIN B COLLOIDAL DISPERSION IN AN ALLOGENEIC BONE MARROW TRANSPLANT RECIPIENT

**Case report.** A 16-year-old boy was diagnosed as having acute T cell lymphoblastic leukemia in July, 1998. Intensive chemotherapy, in another country, with a protocol Berlin-Frankfurt-Munster-oriented for acute T cell lymphoblastic leukemia led to complete remission that lasted until October, 1998. That same month he experienced a hematologic relapse and was treated with a new induction regimen that led to a second complete remission.

Allogeneic bone marrow transplant from his HLA-identical sister was performed in December, 1998, after a conditioning regimen with total body irradiation (1.2 Gy in six refracted doses), etoposide 60 mg/kg and cyclophosphamide 50 mg/kg for 2 days.

He received antiinfective prophylaxis with acyclovir, fluconazole and cyclosporin A (2 mg/kg iv) for graft *vs.* host disease prophylaxis.

On the second posttransplant day the patient developed fever during severe granulocytopenia (polymorphonuclear cells, 100/$\mu$l) and was given antibiotic therapy with meropenem. A viridans streptococcus was recovered from blood culture.

On Day 11 fever and severe granulocytopenia persisted, and the patient was given amphotericin B colloidal dispersion (ABCD; Amphocil) in a 1-mg/kg daily dose. When starting ABCD arterial pressure, cardiac rate, breath rate and creatine kinase were normal.

At the end of 90 min of ABCD infusion, the patient developed severe chills, severe hyperthermia (41.6°C), trismus and generalized muscular hypertonus without loss of consciousness. Arterial blood pressure was 95/30 mm Hg, pulse rate 205 beats/min, respiratory rate 50/min and the $O_2$ saturation 95%.

Administration of hydrocortisone 750 mg iv, diazepam 10 mg iv, acetaminophen 1 g iv, dopamine 5 $\mu$g/kg/min and hydration resulted in a mild improvement.

Thirty minutes later the patient, in continuous severe hyperthermia (>39.5°C), experienced a new episode of severe chills and trismus with loss of consciousness. Treatment with diazepam 20 mg iv and diclofenac 75 mg iv partially controlled his symptoms. A cranial CT scan was normal and his vital signs were normal. During the afternoon the boy sweated profusely and was drowsy. The temperature was 39°C.

At 6 p.m. (5 h after the onset of hyperthermia), despite the supportive therapy of dopamine and rehydration, the patient developed profuse sweating, cyanosis, dyspnea and anuria. The peripheral pulse became progressively undetectable and arterial pressure fell uncontrollably until no longer detectable. He was transferred to the intensive care unit for shock, myoglobinuria and elevated creatine phosphokinase value of 21 730 units.

Initially the patient had severe muscular pain and needed ventilatory assistance for 10 days because of paralysis of the respiratory muscles. Daily chest radiographs were normal. The general condition gradually improved and muscle enzyme values returned to normal in 7 days with complete resolution of muscular problems.

Engraftment occurred during intensive treatment and Grade I graft *vs.* host disease resolved with corticosteroids iv.

No signs of muscle damage or neuropathy were present at examination 180 days later.

**Discussion.** Severe rhabdomyolysis is a rare complication of bone marrow transplantation with few cases reported. The reported cases were related to causes such as cytomegalovirus infection,[1, 2] high serum values of cyclosporin A,[3] cyclosporin A with corticosteroids,[3] *Bacillus cereus* infection[4] and other kinds of bacterial agents, grand mal seizure,[3] antituberculous medication[5] and high dose cytarabine therapy.

In our patient the findings of fever, muscular hypertonus, trismus and rhabdomyolysis were consistent with the diagnosis of malignant hyperthermia syndrome. No depolarizing drugs were in use. Additionally cytomegalovirus was not detected before or during the reported episode, cyclosporin A plasma values were normal (221 ng/ml before and 153 ng/ml during the episode) and the serum potassium was 4.4 mEq/l. Numerous infective agents[1, 2, 4] have been associated with rhabdomyolysis, but no microbiologic cultures were positive in this patient at the onset of rhabdomyolysis or during the next few weeks. Creatine kinase concentrations were normal a few hours before the event and rose afterward.

Correlation between rhabdomyolysis with myoglobinuria and amphotericin B was first reported by Drutz et al.[6] in 1970, but in that report the role of hypokalemia was relevant in the cascade of events. White et al.[7] in 1998 reported that infusion-related hypoxia and chills were more common in ABCD recipients than in amphotericin B recipients.

In our patient there was a temporal relation with competition of ABCD infusion and the onset of acute symptomatology, and all drugs were stopped before ABCD to avoid incompatibility. No other known causes of rhabdomyolysis

were found in our patient. As a result we believe that this acute episode can be attributed to a severe reaction to ABCD.

Mario R. Rossi, M.D.
Daniela V. Longoni, M.D.
Attilio M. Rovelli, M.D.
Cornelio Uderzo, M.D.
Ematologia Pediatrica
Clinica Pediatrica dell'Università di Milano-Bicocca
Ospedale "San Gerardo"
Monza, Italy

Accepted for publication Oct. 27, 1999.
Key words: Adverse effect, amphotericin B, rhabdomyolysis.
Address for reprints: M. R. Rossi, M.D., Clinica Pediatrica dell'Università di Milano-Bicocca, Ospedale San Gerardo, via Donizetti 106, 20052 Monza, Italy. Fax 39-039-2301646; E-mail masera@xquasar.it.

1. Maruyama F, Miyazaki H, Ezaki K, et al. Severe rhabdomyolysis as a complication of peripheral blood stem cell transplantation. Bone Marrow Transplant 1994;14:481–2.
2. Hughes GS, Hunt R. Cytomegalovirus infection with rhabdomyolysis and myoglobinuria. Ann Intern Med 1984;101: 276–7.
3. Volin L, Jarventie G, Ruutu T. Fatal rhabdomyolysis as a complication of bone marrow transplantation. Bone Marrow Transplant 1990;6:59–60.
4. Sanfructuoso C, Caballero MD, Vazquez L, et al. Rhabdomyolysis associated with septicemia after autologous bone marrow transplantation. Bone Marrow Transplant 1997;19:97.
5. Jackson SR, Barnett MJ, Keller O, et al. Recovery from rhabdomyolysis after allogeneic BMT: report of a case with speculation on causation. Bone Marrow Transplant 1995;15: 803–4.
6. Drutz DJ, Fan LH, Tai TY, et al. Hypokalemic rhabdomyolysis and myoglobinuria following amphotericin B therapy. JAMA 1970;211:824–6.
7. White MH, Bouwden RA, Sandler ES, et al. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion *vs.* amphotericin B in the empirical treatment of fever and neutropenia. Clin Infect Dis 1998;27:296–302.

## HUMAN MONOCYTIC EHRLICHIOSIS IN A CHILD WITH LEUKEMIA

In the last few years human monocytic ehrlichiosis (HME) has been increasingly reported in children. The disease is often initially unrecognized and is known to have a wide range of clinical severity.[1] Although concomitant HME and significant underlying disease has been described in adults, the majority of affected children have been previously healthy.[2] Therefore there is little experience with the diagnosis and treatment in children with underlying illnesses. We recently cared for a child with pre-B cell leukemia who developed HME shortly after initiation of induction chemotherapy. The patient had a severe and prolonged disease course, with a slow recovery. The diagnosis of HME in the immunocompromised host may be difficult to establish and often requires specific diagnostic tests for *Ehrlichia chaffeensis*.

**Case report.** A 6-year-old boy from the Eastern Shore of Maryland was admitted in July, 1998, with fever, abdominal pain and fatigue. The patient had recently been diagnosed with pre-B cell lymphoblastic leukemia after biopsy of an enlarged postauricular lymph node. A bone marrow biopsy did not reveal leukemic involvement.

One week before admission a central venous catheter was placed, and induction chemotherapy was started with vincristine, asparaginase and prednisone. Because of a prior allergic reaction to trimethoprim-sulfamethoxasole, oral dapsone was used for *Pneumocystis carinii* pneumonia prophylaxis. Three days after placing the central venous catheter, emesis and fever appeared. There was no cough, headache, sore throat, rash or diarrhea. Fever persisted and the child was admitted for evaluation. In the month before admission he had been exposed to dogs, cats, mice and a fresh water pond, but no tick bites were noted.

Physical examination on admission revealed an ill-appearing child without an obvious source for the fever. Complete blood count showed white blood cell count (WBC) 3100/mm$^3$ (3% bands, 91% polymorphonuclear, 6% lymphocytes), hemoglobin (Hb) 11.6 g/dl, platelets 92 000/mm$^3$. Blood, urine and throat cultures were obtained, and therapy with piperacillin/tazobactam was started.

During the next 5 days fever and abdominal pain worsened despite broadening the antimicrobial therapy with amikacin, oxacillin and metronidazole. Abdominal ultrasound revealed increased thickness of the gallbladder wall, with sludge in the gallbladder, as well as a moderate amount of fluid in the pelvis. Because the patient was receiving broad spectrum antibiotic therapy for several days, with worsening of his clinical situation, infectious disease specialists were consulted

On examination the temperature was 39.5°C. The child was irritable. There was a new erythrodermal rash on the face and trunk, periorbital edema and cracked lips. Heart and lung examination was normal. The abdomen was mildly tender; the liver was palpated 6 cm below the costal margin without splenomegaly. A few hours later, tonic-clonic seizures were followed by encephalopathy, and a new gallop rhythm was noted. Repeat complete blood count showed WBC 400/mm$^3$, Hb 7.8 g/dl and platelet count 58 000/mm$^3$. Although the patient had both absolute lymphopenia (200/mm$^3$) and absolute neutropenia (200/mm$^3$), it was noted that the patient's level of neutropenia and anemia were greater than expected for the amount of induction chemotherapy he had received. The aspartate aminotransferase was 1276 IU/l, alanine aminotransferase 318 IU/l, albumin 2.1 g/dl and total bilirubin 2.5 g/dl with direct bilirubin of 1.7 g/dl. The creatinine was 1.7 mg/dl, the serum sodium was 128 mEq/l, serum potassium was 3.6 mEq/l and triglycerides were 872 mg/dl. Prothrombin time was 13.7 s and activated partial thromboplastin time was 62.5 s. Head computerized tomography demonstrated no signs of intracranial hemorrhage or mass effect. Cerebrospinal fluid (CSF) examination revealed 28 WBC/mm$^3$ (100% monocytes), 18 red blood cells/mm$^3$, protein 35 mg/dl and glucose 65 mg/dl. Urinalysis showed 1 to 2 WBC and 1 red blood cell/high power field and 4+ protein. Abdominal computerized tomography revealed an enlarged liver without abscess.

Further diagnostic tests included viral cultures from stool, urine and throat; urine PCR for leptospirosis; and blood PCR for ehrlichioses. Piperacillin-tazobactam, dapsone, vincristine and asparaginase were discontinued; doxycycline 4 mg/kg/day and vancomycin were started; amikacin and metronidazole were continued.

Three days after starting doxycycline, the child was afebrile, communicated again with his parents and reported decreased abdominal pain. The jaundice and the gallop rhythm disappeared. The edema attributed to hypoalbuminemia secondary to nephrotic syndrome improved with fluid restriction, albumin and furosemide. Liver function tests normalized. However, the patient developed persistent hyponatremia that gradually corrected with saline boluses. One year after the acute episode the patient is completing his maintenance chemotherapy. Dapsone prophylaxis for *P. cari-*

*nii* pneumonia was not restarted. Bilateral foot drop improved over several months.

Multiple bacterial, viral and fungal cultures as well as serologic studies for hepatitis A, B and C viruses and Epstein-Barr virus were all negative. Urine PCR for leptospirosis was negative. A modified PCR protocol for identification of *E. chaffeensis* DNA in blood[3] was positive. To exclude amplicon contamination a PCR using universal primers for eubacterial 16S ribosomal RNA genes[4] revealed a 1478-bp sequence that was 99.8% identical with that of E. *chaffeensis*. The results strongly suggested that *E. chaffeensis* was present in the blood and was the etiologic agent of this child's illness. Despite the lack of plasma *E. chaffeensis*-reactive antibodies in acute phase and in early convalescence 3 weeks later, a repeat test 11 months later showed a titer of 1280.

The possibility of reactivation of a persistent infection was raised. Immunohistochemical stains were performed on the lymph node biopsy obtained before chemotherapy using *E. chaffeensis* monoclonal and polyclonal antibodies, but no ehrlichiae were detected.

**Discussion.** This case illustrates the difficulty of diagnosis of HME in a child with a complicated illness such as leukemia and underscores the broad clinical spectrum of disease manifestations with *E. chaffeensis* infection. The child's febrile illness appeared shortly after initiation of induction chemotherapy, performed on an outpatient basis when tick exposure is most likely to have occurred. The fever, fatigue, abdominal pain and elevated liver function tests were initially attributed to central venous catheter sepsis, infectious hepatitis or other intraabdominal process prompting broad spectrum antibiotic therapy. Fever persisted and within several days a multiorgan disease developed, including fever, rash, hepatitis, meningoencephalitis, nephrotic syndrome and coagulopathy. A variety of infectious etiologies, Kawasaki disease and an adverse drug reaction were considered.

Dapsone use has been associated with a rare hypersensitivity-like reaction known as "dapsone syndrome."[5] Symptoms of fever, nausea, vomiting and rash usually begin 2 to 6 weeks after initiation of dapsone therapy. Within several days hepatomegaly, lymphadenopathy and jaundice might develop. Laboratory abnormalities include anemia (often hemolytic), lymphocytosis, eosinophilia and elevated liver function tests. CSF pleocytosis has been described as well.[6] Some cases may progress to multiorgan failure and death. Clinical resolution typically occurs within several days after cessation of dapsone. Our patient, however, did not show a typical presentation of dapsone syndrome.

The broad exposure history combined with acute multiorgan disease expanded the differential diagnoses to include leptospirosis, ehrlichioses and Rocky Mountain spotted fever. The genus *Ehrlichia* is composed of obligate, intracellular, Gram-negative pleomorphic coccobacilli transmitted by ticks. Most cases occur from May through July in rural areas.[7] About 75% of children report tick exposure or bite.[1, 8] However, the absence of tick bite history should not exclude the diagnosis whenever clinically suspected. Typical clinical manifestations include fever, headache, myalgias and gastrointestinal symptoms. Rash is more often a feature in children but may be subtle and present late in the course. Other symptoms and signs include nuchal rigidity, adenopathy, photophobia, conjunctivitis, pharyngitis and edema of the hands or face. Hepatosplenomegaly is a common finding.[1, 2, 8] The occurrence of foot drop is an infrequent late complication of HME in children and adults, probably resulting from perineural inflammation that is slow to resolve. Foot drop is also a well-recognized complication of vincristine therapy; thus it is plausible that the combined effects of HME and chemotherapy resulted in the relatively more severe neurologic abnormality experienced by this patient.

Although persistent infection of animals with *E. chaffeensis* is well-documented, persistence in humans is rare.[9] The lack of antibodies at the onset of induction chemotherapy and the inability to demonstrate *E. chaffeensis* by immunohistologic studies in lymphoid tissues obtained at the time when the original hematologic malignancy diagnosis was rendered strongly suggest primary infection and not reactivation of persistent or latent infection.

Laboratory studies show a characteristic profile of leukopenia, with absolute lymphopenia and neutropenia, thrombocytopenia and mild anemia.[10] Hyponatremia and elevated serum transaminase values are also frequent. Renal involvement may occur and can be associated with severe disease and prolonged hospitalization. The few children for whom lumbar punctures were performed have been found to have CSF examinations consistent with aseptic meningitis.[11] In situations such as induction chemotherapy where leukopenia is anticipated, differentiation between monocytic ehrlichiosis and the effects of the chemotherapeutic agents may not be possible. However, in this case the child demonstrated the typical pattern observed with HME of early lymphopenia followed by neutropenia disproportionate to chemotherapy.

The diagnosis is usually established by demonstration of *E. chaffeensis* antibody titers of $\geq$64 or with a 4-fold or greater change in titers between acute and convalescent sera using indirect fluorescent antibody testing. The child's underlying disease and chemotherapy may explain the initial lack of a rising titer of *E. chaffeensis* antibodies in serum. PCR is a sensitive and specific test for the diagnosis of HME,[3] and in the immunocompromised population may be a valuable diagnostic tool.

With the expansion of the immunocompromised population along with the increased use of outpatient therapeutic strategies, a broader range of potential infectious exposures should be considered in episodes of fever and neutropenia. Moreover, HME may be difficult to diagnose in children with underlying immunodeficiencies. By mimicking adverse drug reactions clinical diagnosis can be missed, and the laboratory diagnosis may be difficult to establish by routine serologic tests. Whenever suspected clinically, doxycycline therapy should be instituted and may be lifesaving.

**Acknowledgment.** We thank Neal Halsey, M.D., for valuable discussions regarding the diagnosis of the patient.

Ravit Arav-Boger, M.D.
Julia H. Knepp, M.S.
Jennifer J. Walls, M.S.
J. Stephen Dumler, M.D.
Division of Pediatric Infectious Diseases
Department of Pediatrics (RAB)
Division of Medical Microbiology
Department of Pathology (WHK, JJW, JSD)
The Johns Hopkins University School of Medicine
Baltimore, MD

Accepted for publication Oct. 19, 1999.
Key words: Human monocytic ehrlichiosis, polymerase chain reaction, leukemia, *Ehrlichia chaffeensis*.

Address for reprints: Ravit Arav-Boger, M.D., The Johns Hopkins University, Department of Pediatrics, Division of Infectious Diseases, 600 North Wolfe Street/Park 256, Baltimore, MD 21287-4933. Fax 410-614-1491; E-mail boger@welchlink.welch.jhu.edu.

1. Jacobs RF, Schutze GE. Ehrlichiosis in children. J Pediatr 1997;131:184–92.
2. Schutze GE, Jacobs RF. Human monocytic ehrlichiosis in

children. Pediatrics 1997;100:e10.
3. Anderson BE, Sumner JS, Dawson JE, et al. Detection of the etiologic agent of human ehrlichiosis by polymerase chain reaction. J Clin Microbiol 1992;30:775–80.
4. Anderson BE, Dawson JE, Jones DC, Wilson KH. *Ehrlichia chaffeensis,* a new species associated with human ehrlichiosis. J Clin Microbiol 1991;29:2838–42.
5. Johnson DA, Cattau EL, Kuritsky JN, Zimmerman HJ. Liver involvement in the sulfone syndrome. Arch Intern Med 1986; 146:875–7.
6. Corp CC, Ghishan FK. The sulfone syndrome complicated by pancreatitis and pleural effusion in an adolescent receiving dapsone for treatment of acne vulgaris. J Pediatr Gastroenterol Nutr 1998;26:103–6.
7. Dumler JS. Ehrlichioses: emerging infections. Curr Opin Infect Dis 1998;11:183–7.
8. Edwards MS. Ehrlichiosis in children. Semin Pediatr Infect Dis 1994;5:143–7.
9. Dumler JS, Sutker WL, Walker DH. Persistent infection with *Ehrlichia chaffeensis.* Clin Infect Dis 1993;17:903–5.
10. Fishbein DB, Dawson JE, Robinson LE. Human ehrlichiosis in the United States, 1985 to 1990. Ann Intern Med 1994; 120:736–43.
11. Berry DS, Miller RS, Hooke JA, Massung RF, Bennett J, Ottolini MG. Ehrlichial meningitis with cerebrospinal fluid morulae. Pediatr Infect Dis J 1999;18:552–5.

# Your Diagnosis, Please

EDITED BY PARVIN H. AZIMI, M.D. AND MOSES GROSSMAN, M.D.

### ELEVEN-MONTH-OLD WITH RECURRENT BACTERIAL AND ASEPTIC MENINGITIS

An 11-month-old developmentally appropriate Caucasian boy was admitted to the University of California San Francisco Medical Center because of recurrent meningitis. He was born at term after an uncomplicated pregnancy and labor and delivery. He was discharged at 48 h. At 2 weeks of age he presented with fever and was evaluated for sepsis. The cerebrospinal fluid culture (CSF) grew *Staphylococcus aureus*, and the patient received intravenous gentamicin for 11 days as monotherapy with good response. At 6 weeks he had a recurrent episode of fever and again the CSF culture grew *S. aureus* for which the patient received 30 days of treatment with intravenous nafcillin and gentamicin. One week after the completion of therapy, the patient had a 24-h episode of fever, emesis and irritability that resolved spontaneously.

After the second episode of meningitis the patient was evaluated by an immunologist and found to have low immunoglobulins (IgG 148 mg/dl, IgM 49.2 mg/dl, IgA <6.7 mg/dl, IgE <4 mg/dl). He was diagnosed with probable transient hypogammaglobulinemia of infancy and started on therapy with intravenous immunoglobulin. During the subsequent months he continued to have recurrent episodes of fever, as high as 104°F (40°C), with emesis, irritability and extensor posturing. Most episodes resolved within 24 to 48 h without treatment. The mother initially reported that these episodes occurred 4 to 5 days before the infant was to receive intravenous immunoglobulin; however, subsequent history suggested a more sporadic pattern.

Two weeks before the current admission, the patient had been admitted to the hospital for fever and emesis, and he received intravenous fluids and antibiotics. He was discharged after 1 week with a diagnosis of viral syndrome. The current admission was scheduled through the immunology service to further evaluate the patient's syndrome.

The night of admission the patient had a fever of 100.6°F (38.1°C), emesis and irritability. The physical examination was significant only for meningismus. Laboratory evaluation included a normal complete blood count and a lumbar puncture with the following CSF findings: glucose 18 mg/dl, protein 89 mg/dl, red blood cell count 232 cells/ml, white blood cell count (WBC) 2875 cells/ml [86% polymorphonuclear cells (PMNs), 6% lymphocytes, 7% large lymphocytes]. A Gram-stained smear was positive for numerous PMNs and mononuclear cells, but no organisms were seen. Therapy was started with nafcillin and cefotaxime and responded within 24 h with complete resolution of fever and meningismus. Blood culture and CSF culture had no growth.

Four days later while receiving antimicrobial therapy, the patient had a recurrent episode of fever (39.1°C) and meningismus. Repeat laboratory evaluation showed an elevated peripheral WBC count (16 300 cells/ml) with a left shift and a lumbar puncture with the following results: 19 mg/dl, protein 205 mg/dl, red blood cell count 41 cells/ml, WBC 3300 cells/ml (98% PMNs, 2% lymphocytes), A Gram-stained smear was positive for numerous PMNs and mononuclear cells, but no organisms were seen. Nafcillin was stopped and vancomycin and rifampin were started; cefotaxime therapy continued. The patient's symptoms resolved within 24 h.

An infectious disease consult was obtained. Further history and physical examination and a single test revealed the diagnosis. Appropriate therapy led to complete resolution of the patient's syndrome.

Kevin A. Slavin, M.D.*
Steve Kohl, M.D.†
Divisions of Pediatric Infectious Diseases and Clinical Pharmacology and Experimental Therapeutics
University of California San Francisco (KAS)

Pediatric Infectious Diseases
University of California San Francisco
San Francisco General Hospital (SK)

San Francisco, CA

Accepted for publication Oct. 19, 1999.

*Current address: 300 Prospect Avenue, Penthouse D, Hackensack, NJ 07601.

†Current address: Department of Pediatrics, Oregon Health Sciences University, Portland, OR.

*For denouement see p. 178.*

# Letters

### SERUM ALPHA-TOCOPHEROL AND BETA-CAROTENE LEVELS ARE NOT ASSOCIATED WITH RHEUMATIC FEVER IN BANGLADESHI CHILDREN

To The Editors:

Rheumatic fever is a nonsuppurative sequel of group A beta-hemolytic streptococcal throat infection. It is not clear why only a few of those affected develop rheumatic fever after group A streptococcal infection (1 to 3%).[1] Many researchers