Your Diagnosis, Please

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

THREE-YEAR-OLD GIRL WITH FEVER AND COMA

A 3-year-old Caucasian-Hispanic girl was transferred to Children's Hospital Oakland in a coma. She was healthy until 10 days before transfer, when she developed high fever up to 39.5°C, fatigue and emesis but no diarrhea. On Day 6 of her febrile illness, she was hospitalized in another hospital with a diagnosis of acute gastroenteritis with dehydration. On Day 2 of this hospitalization she had a generalized tonic-clonic seizure. A computed tomography scan of the head was normal. Lumbar puncture revealed cerebrospinal fluid (CSF) pleocytosis with 540 white blood cells/mm^3, 90% neutrophils, 10% lymphocytes, protein of 122 mg/dl and glucose of 47 mg/dl. An electroencephalogram was normal. The patient was treated with acyclovir and Dilantin but remained febrile and intermittently lethargic. A magnetic resonance imaging scan of the head was obtained on Day 10 of her febrile illness and showed marked ventriculomegaly with patent fourth ventricle suggesting communicating hydrocephalus, and a few areas of focal increased signal within the right posterior frontal and temporal cerebral cortex. For this study the patient was sedated with chloral hydrate. Immediately after the magnetic resonance imaging scan she had another seizure, followed by somnolence, development of pinpoint pupils, loss of light and gag reflexes. She was intubated, received one dose of ceftriaxone and was transferred to the pediatric intensive care unit at Children's Hospital Oakland.

Her past medical history was unremarkable, except for a recent episode of acute otitis media, which was treated with amoxicillin for 10 days. Her mother had a history of alcohol abuse, and the patient's primary caretakers and legal guardians were her maternal grandparents. The family history was significant for systemic lupus erythematosus in three maternal great aunts. There was a 4-year-old cat in the household, and the patient had been observed to play in the litter box. The family had recently acquired a parakeet and cockatiel, and they had an aquarium with fish. There was no history of camping or swimming. There was no known exposure history to tuberculosis, but there was exposure to a close family friend with chronic cough.

Physical examination demonstrated a comatose, intubated, ventilated child. Her temperature was 38.2°C, heart rate 138 beats/min, respiratory rate 23 breaths/min and blood pressure 111/67 mm Hg. Neurologic examination revealed pinpoint pupils, which were nonreactive to light, absent gag and corneal reflexes, no response to sternal rub and withdrawal of extremities in response to painful stimuli of hands or feet. Deep tendon reflexes were hyperactive and symmetric. Head and neck examination were otherwise unremarkable; chest, cardiovascular, abdominal, external genital and skin examination were normal.

The peripheral white blood cell count was 8700/mm^3 with 63% segmented neutrophils, 7% band forms, 16% lymphocytes, 13% monocytes and 1% eosinophils. Hemoglobin was 10.8 g/dl. Platelet count was 340 000/mm^3. Serum electrolytes, blood urea nitrogen, creatinine, liver function tests, total protein, albumin, ammonia, coagulation studies and urinalysis were all normal. Blood and CSF cultures before treatment with ceftriaxone from the other hospital were negative.

The patient had placement of an external ventricular drain to treat the hydrocephalus shortly after arrival at Children's Hospital Oakland but had no improvement in her neurologic status. CSF analysis of the ventricular fluid revealed a white blood cell count of 3/mm^3, red blood cell count of 96/mm^3, protein of 44 mg/dl and glucose of 53 mg/dl. Repeat lumbar puncture on hospital Day 2 showed a white blood cell count of 354/mm^3 with 46% neutrophils, 48% lymphocytes, 5% monocytes and 1% basophils; protein was 1247 mg/dl; glucose was 6 mg/dl; and lactic acid was 6.0 mEq/l.

Multiple stains and cultures for acid-fast bacilli from CSF and respiratory secretions were negative. PCRs for *Mycobacterium tuberculosis* on ventricular and spinal fluid were also negative. Skin tests with purified protein derivative (PPD) and *Candida* antigen showed no induration and ~5 mm induration, respectively. There were no areas of infiltrate or atelectasis on her initial chest radiograph. All household contacts had negative PPD skin tests and symptom reviews for tuberculosis. PPD skin test and chest radiography on the family friend with chronic cough were both negative.

Multiple bacterial and fungal cultures from blood and CSF were negative. Serologic tests for *Toxoplasma gondii*, *Coccidioides immitis*, *Mycoplasma pneumoniae*, *Bartonella henselae* and *quintana*, and human immunodeficiency virus were all negative. Antigen testing for *Cryptococcus neoformans* on blood and CSF was negative. PCR for human herpes simplex virus on CSF was negative. Serum concentrations of very long chain fatty acids and copper were normal. Serum arsenic level was <10 μg/l. Antinuclear antibodies were negative; erythrocyte sedimentation rate (Westergren) was 38 mm/h. Ophthalmologic examination revealed normal fundi and cornea.

The patient was empirically treated for tuberculous meningitis with isoniazid, rifampin, ethambutol and pyrazinamide via nasogastric tube, as well as intravenous methylprednisolone. Ceftriaxone and acyclovir were continued for 14 and 3 days, respectively.

The patient defervesced on Hospital Day 2 but continued to be comatose. On Day 24 of her illness an electroencephalogram documented electrocerebral silence consistent with the clinical diagnosis of brain death. Supportive care was withdrawn the following day, in agreement with her family. Shortly before her death another blood test and lumbar puncture revealed the diagnosis, which was confirmed by autopsy.

Anna Bakardjiev, M.D.
Carol Glaser, D.V.M., M.D.
Fred Schuster, Ph.D.
Govinda S. Visvesvara, Ph.D.

Division of Infectious Diseases
Children's Hospital Oakland
Oakland, CA (AB)

Viral and Rickettsial Disease Branch
Division of Communicable Disease Control
State of California Department of Human Health Services
Richmond, CA (CG, FS)

Division of Parasitic Diseases
Centers for Disease Control and Prevention
Atlanta, GA (GSV)

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Brief Reports

CLINICAL COURSES OF CROUP CAUSED BY INFLUENZA AND PARAINFLUENZA VIRUSES

Influenza viruses have occasionally been associated with severe manifestations of croup, but no comparative studies of different viral etiologies are available. In a retrospective study we compared the clinical courses of croup caused by influenza and parainfluenza viruses in hospitalized children. By several indicators the clinical picture of croup caused by influenza viruses was significantly more severe than that caused by parainfluenza viruses.

Croup (laryngotracheobronchitis) is a common respiratory tract infection in children. The highest incidence, 3 to 5 cases per 100 children, occurs during the second year of life.[1] Croup accounts for ~15% of all lower respiratory tract infections in children, and 35% of those occurring during the first 2 years of life.[1, 2] Although croup is a relatively mild disease in the majority of cases, the clinical presentation is occasionally severe, and hospitalization rates of 1.3 to 2.6% have been reported.[1, 2] In the United States croup has been estimated to cause 41 000 hospitalizations yearly.[3]

Parainfluenza virus types 1, 2 and 3 are the most frequent etiologic agents in croup, accounting for approximately two-thirds of cases with known etiology.[1, 4, 5] Other etiologic agents include influenza viruses, respiratory syncytial virus, adenovirus and rhinovirus. In a 19-year study,[6] influenza A or B viruses were detected in 14% of all children hospitalized with croup, but during the peak months of 13 consecutive influenza epidemics, influenza A infection was documented in 67% of croup patients. In another study[7] croup was the clinical presentation in 8% of children hospitalized with influenza.

Although some reports have associated influenza viruses with severe manifestations of croup,[8, 9] no comparison of the clinical presentation of croup caused by influenza and parainfluenza viruses is available. We sought to investigate whether the clinical picture of croup caused by influenza viruses differs from that caused by parainfluenza viruses in hospitalized children.

Methods. This retrospective study included children hospitalized at the Department of Pediatrics, Turku University Hospital, during 1980 through 1999. The average number of children with croup as the discharge diagnosis was 95 per year. However, nasopharyngeal aspirates for viral detection were obtained from only a minority of croup patients as part of clinical practice, not according to any prespecified criteria. The medical records of all croup patients with a positive finding for either influenza or parainfluenza virus infection were reviewed. The diagnosis of croup was considered validated if inspiratory stridor or distress and/or hoarseness or barking cough were recorded, and no other explanation for the symptoms was available. Because some children with influenza croup might have been discharged with the diagnosis of influenza instead of croup, we also checked the medical records of all influenza-positive children regardless of the discharge diagnosis. In this way we identified 4 additional children with croup caused by influenza viruses.

All children in both groups were managed according to generally accepted methods without any knowledge of this study. The clinical data collected from the medical records included age, gender, presence of chronic illnesses or other underlying conditions, duration of fever and other symptoms before hospitalization, occurrence of febrile convulsions, length of hospital stay, highest measured temperature and duration of fever in hospital, presence of acute otitis media or pneumonia, treatment with inhaled epinephrine or glucocorticoids (inhaled, oral or parenteral), need for supplemental oxygen or tracheal intubation and treatment at the intensive care unit. Only radiologically confirmed cases of pneumonia were included in this analysis.

During the study years the primary method for the detection of influenza A and B and parainfluenza type 1, 2 and 3 viruses was antigen detection by radioimmunoassay, immunofluorescence, enzyme immunoassay or time-resolved fluoroimmunoassay.[10] In a few children the documentation of the viral etiology was based on viral culture or routine serologic methods.

The Mann-Whitney *U* test, the *t* test and the chi square test were used to compare differences between the groups.

Results. Twenty-nine children had croup caused by influenza viruses (influenza A, 23; influenza B, 3; type unknown, 3), and 88 children had croup caused by parainfluenza viruses (type 1, 33; type 2, 26; type 3, 29). No marked differences were observed among the children with parainfluenza type 1, 2, or 3 croup (data not shown). The demographic characteristics of children with influenza and parainfluenza croup were comparable (Table 1). Boys were affected more often than girls in both groups. The median duration of respiratory symptoms or fever before hospitalization was 1 day in both groups.

The median duration of hospitalization was significantly longer in children with influenza croup (4 days) than in those with parainfluenza croup (2 days; $P = 0.001$). After the initial discharge from the hospital, children with influenza croup had a 4-fold higher rate of readmission because of relapsing inspiratory distress during the next few days than did children with parainfluenza croup (21% *vs.* 5%; $P = 0.02$). During the hospital stay inhaled epinephrine was used more frequently in children with influenza (48%) than in those with parainfluenza croup (11%; $P < 0.001$). Children with influenza croup received glucocorticoids more commonly and for a

TABLE 1. Demographic and clinical data of children with influenza or parainfluenza croup

Characteristic	No. of Children*		*P*
	Influenza ($N = 29$)	Parainfluenza ($N = 88$)	
Age, median (range), yr	1.7 (0.6–10.0)	1.4 (0.03–14.1)	0.12
Boys	18 (62)†	61 (69)	0.62
Underlying condition‡	5 (17)	6 (7)	0.19
Hospital stay, median (range), days	4 (1–11)	2 (1–27)	0.001
Readmission to hospital	6 (21)	4 (5)	0.02
Inhaled epinephrine	14 (48)	10 (11)	<0.001
Steroid treatment	18 (62)	28 (32)	0.008
Duration of steroid treatment, median (range), days	3 (1–6)	1 (1–17)	<0.001
Supplemental oxygen	7 (24)	3 (3)	0.002
Intensive care unit	8 (28)	10 (11)	0.07
Endotracheal intubation	2 (7)	3 (3)	0.78
Acute otitis media	13 (45)	15 (17)	0.005
Pneumonia	5 (17)	3 (3)	0.03
Fever ≥39°C	19 (66)	34 (40)§	0.03

* Values represent number of children, unless otherwise stated.

† Numbers in parentheses, percent, unless otherwise stated.

‡ Asthma, prematurity, Down's syndrome, Rubinstein's syndrome, mental retardation, or fetal alcohol syndrome.

§ Data not available for three children.

longer period and needed supplemental oxygen more frequently than children with parainfluenza infection. Tracheal intubation was rarely needed in either group.

With respect to clinical findings unrelated to the severity of croup, acute otitis media was diagnosed in almost one-half (45%) of the children with influenza croup, compared with 17% of those with parainfluenza croup ($P = 0.005$). Also pneumonia occurred more frequently in children with influenza croup. During the hospital stay 66% of children with influenza croup had fever ≥39.0°C, compared with 40% of children with parainfluenza croup ($P = 0.03$). The mean highest measured temperatures in children with influenza and parainfluenza croup were 39.2°C and 38.6°C, respectively ($P = 0.002$).

All results remained essentially unchanged even when children with underlying conditions were excluded from the analyses.

Discussion. This study demonstrates that the clinical picture of croup caused by influenza viruses is substantially more severe than that caused by parainfluenza viruses in hospitalized children. Children with influenza croup stayed longer in the hospital, and after initial discharge the risk of readmission was substantially greater in children with influenza infection. These findings could be partly explained by the well-known features of influenza infection that are not directly related to croup: high and long-lasting fever; and frequent development of pneumonia or other complications. However, all readmissions occurred because of relapsing laryngeal symptoms, not because of development of bacterial complications. In the retrospective setting we were unable to obtain reliable data about the degree of dyspnea. However, inhaled epinephrine and glucocorticoids are clearly used for the management of inspiratory airway obstruction, and the more frequent use of these drugs in children with influenza than with parainfluenza croup provides evidence for the severity of the symptoms of croup in children with influenza infection.

The typical clinical presentation of croup including inspiratory stridor, barking cough and hoarseness is easy to distinguish, which increases the reliability of the discharge diagnoses in the medical records. Even in the case of influenza croup, most children had the discharge diagnosis of croup instead of influenza. When interpreting the results of this study, it should be noted that virologic samples were not taken systematically from all children with croup, and it is probable that children with more severe manifestations of the disease were overrepresented in the study population. However, this should not bias the comparison between children with positive findings for influenza or parainfluenza viruses. The nasopharyngeal specimens were obtained on clinical grounds alone, without any knowledge of this analysis at that time. Therefore we consider our main findings reliable in the setting of hospitalized children. However, it is not known whether there are differences between influenza and parainfluenza croup in the majority of children who are managed as outpatients.

Antigen detection of influenza and parainfluenza viruses is possible within 1 day in the laboratory, and for influenza rapid point-of-care tests are currently available. Although the treatment of croup with glucocorticoids and eventually with inhaled epinephrine is similar irrespective of the etiology, detection of the causing virus might be beneficial for the clinical management of the children. If influenza is diagnosed within 48 h of the onset of symptoms, specific antiviral therapy with a neuraminidase inhibitor could be considered. A recent study demonstrated that oral oseltamivir treatment shortened the duration of symptoms of influenza and reduced the development of acute otitis media as a complication in children.[11]

Influenza epidemics are associated with substantial numbers of excess hospitalizations and outpatient visits in young children.[12, 13] The recently developed intranasal, live attenuated influenza vaccine[14] could be anticipated to lower the threshold of influenza vaccination in children. Although croup is a relatively rare manifestation of influenza infection, the results of the present study indicate that the severity of croup caused by influenza viruses is greater than average, which lends support to the idea of more widespread use of influenza vaccine in children.

Ville Peltola, M.D.
Terho Heikkinen, M.D.
Olli Ruuskanen, M.D.
Department of Pediatrics
Turku University Hospital
Turku, Finland

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ACUTE RETINAL NECROSIS SYNDROME IN A CHILD

We recently cared for an 11-year-old child with acute retinal necrosis syndrome, an ophthalmologic condition characterized by the triad of anterior uveitis, occlusive retinal vasculitis and progressive peripheral retinal necrosis. Acute retinal necrosis syndrome occurs primarily in nonimmunocompromised adults as a result of reactivated herpes simplex or varicella-zoster virus infection. Antiviral and antiinflammatory therapy appears to reduce the incidence of vision-threatening retinal necrosis and involvement of the contralateral eye.

Acute retinal necrosis syndrome (ARN) is an ophthalmologic condition characterized by a triad of clinical findings including moderate to severe anterior uveitis and vitritis, severe occlusive vasculitis of the arteries of the retina and progressive peripheral retinal necrosis.[1–4] The usual age of patients with ARN is 20 to 60 years; children have only rarely been reported to have ARN.[5, 6] In addition although ARN is well-described in the ophthalmologic literature, there are very few descriptions reported in the pediatric or internal medicine literature. We recently cared for a child with ARN and describe his case along with a brief review of the current literature[1–29] to familiarize pediatricians with this uncommon but serious illness.

Case report. An 11-year-old boy complained of right eye pain on movement and blurred vision for 6 days before admission. He noted progressive decrease in visual acuity and color distinction. Three days before admission the eye became red, irritated, swollen and more painful, but without associated photophobia or excessive tearing. The boy denied joint pain or swelling, fever, rash or trauma to the eye. His past medical history was significant only for chickenpox at age 3 years.

On admission the child had visual acuity of 20/30 in the left eye and 20/100 in the right eye. Right anterior uveitis was also detected, along with "mutton-fat granulomatous" keratitic precipitates on the inferior cornea and 4+ cells and 3+ flare in the anterior chamber. In addition there was hemorrhagic necrosis of the right retina involving the inferior and superior nasal quadrants in the far periphery, vasculitis of the superior temporal vascular arcade and a pale, swollen optic nerve.

Cerebrospinal fluid (CSF) obtained by lumbar puncture showed lymphocytic pleocytosis (24 white blood cells/μl, differential count of 94% lymphocytes and 6% monocytes). The CSF protein and glucose values were normal (59 and 20 mg/dl, respectively), and bacterial, viral and fungal cultures were sterile. Cranial magnetic resonance imaging scan showed borderline abnormally high T_2 weighted signal intensity of the right optic nerve.

After ARN syndrome was diagnosed, treatment was begun with antiinflammatory, antiviral and anticoagulant medication (methylprednisolone 1 g/day iv in two divided doses for 3 days, prednisone 1% ophthalmic drops every 2 h, acyclovir 1500 mg/m^2/day iv in three divided doses for 10 days and aspirin 325 mg every day). The child's symptoms and ocular findings improved rapidly with treatment. Serial ophthalmologic examinations showed decreasing cells and keratitic precipitates in the anterior chamber and minimal temporal extension of the hemorrhagic necrosis. Visual acuity improved to 20/50, and eye movement became painless. The left eye remained unaffected throughout the hospital course. Subsequent laboratory findings included negative blood PCR amplification and IgG antibody tests for cytomegalovirus and negative serum antibody titers for *Leptospira, Toxocara, Histoplasma, Toxoplasma, Bartonella,* syphilis and Lyme disease. Serum IgG antibodies to herpes simplex (HSV) and varicella-zoster (VZV) viruses were present; PCR assays on the CSF for both viruses were negative. The child was discharged to receive oral acyclovir (800 mg every 6 h) for 3 months. He developed a right retinal detachment ~6 weeks after hospitalization and underwent laser therapy demarcation of the retina. After 30 months of follow-up, the left eye had remained disease-free, and his right eye visual acuity was stable at 20/100.

Discussion. *History of ARN.* The acute retinal necrosis syndrome was first described in the Japanese medical literature by Urayama et al.[7] in 1971, who used the term Kirisawa's uveitis for 6 patients who had panuveitis, retinal arteritis progressing to peripheral retinal necrosis and retinal detachment. Within a decade six cases of similar findings but occurring in both eyes simultaneously were described in the US[8] and in the United Kingdom.[9] An entity related to ARN termed progressive outer retinal necrosis or rapidly progressive herpetic retinal necrosis occurs in HIV-infected patients.[2, 3, 10–12] However, ARN itself most often occurs in immunocompetent hosts.

Clinical findings. Scattered case reports of children with ARN have been published,[6, 17–19] but the majority of patients (>80%) have had disease onset at >20 years old, with a mean age of onset of ARN of ~40 years.[5, 23, 24, 27] Patients with typical ARN often have a prodrome of low grade fever, headaches and neck stiffness.[2–4, 13, 14] Conjunctival injection with a ciliary flush is seen in association with moderately painful eye movements. Visual acuity may be diminished, with complaints of hazy vision and floaters.

Ophthalmoscopic examination of the anterior chamber reveals mild to moderate cellular reaction with fine or large "mutton-fat granulomatous" keratitic precipitates. Uveitis and later vitritis can be severe enough to obstruct examination of the posterior pole. The anterior uveitis progresses to panuveitis within several days to 1 to 2 weeks, with retinal necrosis beginning as small patches of retinal whitening termed "thumbprinting." In two-thirds of cases within 5 days the necrosis coalesces and progresses to involve a 360-degree area.[2] In most cases the necrosis remains peripheral, sparing the macula (and thus central vision). Vasoocclusive retinal and choroid vasculitis is associated with the retinal necrosis. Optic nerve atrophy or inflammation is characteristic of ARN, but its presence is not required to satisfy diagnostic criteria.[1] Other than reports of lymphocytic CSF pleocytosis, routine laboratory findings are nonspecific.[2–4, 13, 14]

The most serious complication of ARN syndrome is not the initial uveitis or the vasculitis, but rather the development of full thickness necrotic retinal holes that appear during the recovery phase of the illness. These retinal holes, along with increasing vitreal fibrous traction on the retina, lead to rhegmatogenous retinal detachment that has been reported to occur in 25 to 75% of cases, at a mean time of 65 days after onset.[2, 3, 13, 15] The contralateral eye is affected in ~33% of cases (range, 20 to 70%), usually within the first 4 to 6 weeks of the onset of disease in the original eye.[2, 3] Scattered case reports have noted disease onset in the contralateral eye up to 20 to 30 years later.[16, 17]

Etiology. ARN appears to be a reactivated herpes virus infection, occurring years after the primary infection (either

chickenpox or herpes simplex mucocutaneous disease).[2–5, 18, 27] Rarely ARN occurs as a primary viral necrotizing retinitis, most commonly associated with chickenpox.[2, 4, 19] In 1982 Culbertson et al.[20] first described eosinophilic intranuclear inclusions consistent with herpesvirus infection in the retinal pigment epithelium and vascular endothelium by electron microscopy from an enucleated eye of a patient with ARN. Subsequently histopathologic, immunocytochemical and light and electron microscopic findings indicative of herpesvirus infection were detected in the enucleated eyes from another patient with ARN.[21] A number of other investigators have since demonstrated the intraocular presence of HSV-1, HSV-2, or VZV in patients with ARN by various means, including intraocular antibody synthesis, *in situ* antigen detection and viral culture of vitreal and retinal tissue, *in situ* hybridization of viral DNA and PCR amplification of viral DNA sequences from eye tissue.[2–5, 18, 22, 27] Recently intraocular T lymphocytes of patients with HSV-1-associated ARN were shown to be reactive to HSV-1 tegument proteins.[28, 29] VZV and HSV-1 appear to occur predominantly in patients >25 years of age, whereas HSV-2 is found in those <25 years of age.[5, 27]

Treatment. Because it appears that VZV, HSV-1 and HSV-2 are the etiologic agents of ARN, most ophthalmologists recommend initial treatment with parenteral acyclovir. However, no prospective, randomized, double blind, placebo-controlled trial data exist to confirm the efficacy, length of treatment or dose of acyclovir required. The current recommendation (based on the two studies discussed below) is to give 1500 mg/m^2/day iv in three divided doses for 10 days as early in the disease course as possible, followed by oral acyclovir (800 mg five times a day for an adult) for 3 months.[2, 3, 14, 23–25]

Use of this sequential intravenous/oral regimen by Blumenkranz et al.[23] in an open trial of 12 patients with clinically diagnosed ARN resulted in regression of retinal lesions in a mean of 3.9 days after starting therapy, with complete regression of active disease noted at 32.5 days. No significant progression of retinal lesions was detected after 48 h of iv therapy, and no contralateral eye was affected after a mean follow-up of 14.5 months. The authors concluded that recovery was more rapid in treated patients than that of untreated historical patients.[23] In a retrospective survey of 54 patients with unilateral ARN, Palay et al.[24] demonstrated a 2-fold decrease of disease onset in the contralateral eye from 75% to 35% in those given sequential intravenous and oral acyclovir. However, in neither study did the use of acyclovir affect the amount of vitritis or the frequency of retinal detachment.[2, 23] It would be useful to study acyclovir therapy in a prospective, randomized controlled trial, but the severity and low incidence of the disease, combined with the need for long term follow-up, may prohibit performance of such a study.

Antithrombotic therapy (e.g. heparin or aspirin) has been suggested as an adjunctive treatment for the ophthalmic vasculitis of ARN, because platelet hyperaggregation has been reported.[2, 3, 26] Systemic glucocorticosteroids also have been reported to decrease vitritis and severe intraocular inflammation, but firm data are not available to prove their efficacy against retinal necrosis and detachment.[2, 24]

Surgical therapy of ARN may include prophylactic laser photocoagulation to prevent rhegmatogenous retinal detachment, but data proving efficacy are limited.[2, 24] Once detachment occurs, scleral buckling, vitrectomy with laser photocoagulation or vitreal gas or oil tamponade may be useful.[2, 10, 24]

Prognosis. The long term visual prognosis of ARN varies widely. Several reports have indicated that ~33% of patients are left with 20/200 vision or worse.[13, 23] Even with successful retinal reattachment, only five of nine eyes in one series had visual acuity of 20/200 or better, with the other four eyes having at best a visual acuity of 20/400.[15] On occasion, if the retina remains attached visual acuity of 20/50 or better has been reported.[13] Unlike other types of uveitis, chronic inflammation or episodic bouts do not occur with ARN.[14]

Sharon Chen, M.D.
Geoffrey A. Weinberg, M.D.
Department of Pediatrics (SC, GAW) and Division of Pediatric Infectious Diseases (GAW)
University of Rochester School of Medicine and Dentistry
Rochester, NY

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RECURRENT PURPURA FULMINANS ASSOCIATED WITH DRUG-RESISTANT *STREPTOCOCCUS PNEUMONIAE* INFECTION IN AN ASPLENIC GIRL

We report a case of purpura fulminans associated with drug-resistant *Streptococcus pneumoniae* that responded to ceftriaxone therapy. Ultrasonography of the abdomen and splenic scan revealed the absence of a spleen.

Purpura fulminans is classically defined by ecchymotic skin lesions, fever and hypotension. The majority of cases are associated with meningococcal sepsis but may also be caused by other bacteria, including *Streptococcus pneumoniae* and other streptococci.[1–3] However, there have been no previous reports of purpura fulminans caused by penicillin-nonsusceptible pneumococci. We present here a case of purpura fulminans associated with by drug-resistant *S. pneumoniae* in a child with congenital asplenia.

Case report. A previously healthy 3-year-3-month-old Thai girl was referred to Chulalongkorn Hospital on December 8, 1997, because of fever and purpuric spots for 2 days. After she developed blue lips, cold hands and feet, difficulty in breathing, drowsiness and several purpuric spots on the buttocks, she was admitted to a provincial hospital. Physical examination revealed an irritable girl with central cyanosis and poor tissue perfusion. Blood pressure was 94/53 mm Hg; pulse rate 180/min, respiratory rate 50/min and body temperature 37.5°C. The liver was palpated 2 cm below the right costal margin. Purpuric spots were discerned on the buttocks and legs. A complete blood count showed leukocytosis, neutrophilia and thrombocytopenia. Treatment was initiated with intravenous fluid, dopamine and intravenous ceftriaxone (100 mg/kg/day).

She was referred to Chulalongkorn Hospital on the following day. Physical examination revealed a conscious girl without cyanosis or dyspnea. Vital signs were: body temperature 39.2°C; blood pressure 98/41 mm Hg; pulse rate 140/min; respiratory rate 28/min. The liver was palpated 1.5 cm below the right costal margin. Multiple discrete purpuric spots, 0.5 to 2 cm in diameter, were present on the arms, legs, buttocks and trunk, with some bullous lesions at the left ankle. The remainder of the physical examination was unremarkable. Laboratory examination revealed a hematocrit of 40.6%; white blood cell count 51 700/mm^3 (neutrophils 75%, lymphocytes 24%, atypical lymphocyte 1%); platelet count 27 000/mm^3; normal urine analysis and blood chemistry. A Gram-stained smear of material from a bullous lesions revealed no white blood cells or organisms. Ceftriaxone was continued and the temperature declined, together with an improvement of the skin lesions. On the fourth day after admission, a blood culture taken from the referring hospital was positive for alpha-streptococci. The isolate was sent to the Streptococcus Center, Department of Microbiology, Chulalongkorn Hospital, Bangkok, where *S. pneumoniae* resistant to oxacillin disc was identified. The MICs for penicillin and ceftriaxone, using the Epsilometric test (E-test), were 1.5 and 0.75 μg/ml, respectively. Ceftriaxone was continued for a total course of 2 weeks. The patient was discharged without morbidity.

She presented again with recurrent episodes of purpura fulminans at the ages of 3 years 9 months and 4 years 3 months. Blood cultures were negative. An immunologic evaluation including serum immunoglobulins (IgG, IgA, IgM) and IgG subclass values and complement evaluation revealed normal results for her age. Abdominal ultrasonography performed twice showed the absence of a spleen. Technetium scan was negative for splenic tissue, confirming the diagnosis of asplenia. One dose of 23-valent polysaccharide pneumococcal vaccine (Pneumovax 23; MSD) was given and serum antibody (performed at IBT Reference Laboratory, Lenexa, KS) was assayed 4 weeks after immunization. Responses above reference range were found to 8 of 12 serotypes. In the subsequent 2 years our patient has not developed invasive pneumococcal infections or purpura fulminans.

Discussion. *Neisseria meningitidis* is the most common organism associated with purpura fulminans, but some reports of pneumococcal purpura fulminans have been published.[1, 2] However, to our knowledge our patient is the first reported case of purpura fulminans caused by drug-resistant *S. pneumoniae*.

A previous study has shown that 63% of patients with pneumococcal purpura fulminans have no spleen.[1] We suggest that immunologic investigation including splenic scan should be performed in patients with pneumococcal sepsis especially in those with recurrent episodes. Pneumococcal vaccine should be considered in patients with the absence of splenic tissue even though the antibody response may not be reliable.

Chitsanu Pancharoen, M.D.
Pantipa Chatchatee, M.D.
Jarungchit Ngamphaiboon, M.D.
Usa Thisyakorn, M.D.
Infectious Diseases (CP, UT) and Allergy and Immunology (PC, JN) Units
Department of Pediatrics
Faculty of Medicine
Chulalongkorn University
Bangkok, Thailand

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Key words: Purpura fulminans, *Streptococcus pneumoniae*, antibiotic-resistant, asplenia.

Address for reprints: Dr. Chitsanu Pancharoen, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University Hospital, Rama IV Road, Bangkok 10330, Thailand. Fax (662) 256-4930; E-mail chitsanu.p@chula.ac.th.

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SUPPURATIVE PAROTITIS CAUSED BY ANAEROBIC BACTERIA IN NEWBORNS

Staphylococci are the usual bacterial etiology of suppurative parotitis in newborns. This report describes for the first time recovery of anaerobic bacteria from aspirates of the infected gland in two infants with suppurative parotitis. *Peptostreptococcus intermedius* and *Prevotella melaninogenica* were isolated from one child and *Prevotella intermedia* from the other patient. Complete recovery occurred after 4 weeks of antimicrobial therapy.

Suppurative parotitis is uncommon in newborns.[1–4] The predominant organisms are *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Streptococcus* group B. Although anaerobic bacteria have been recovered from parotid infections in older children[5, 6] and adults,[7] only two case reports describe their recovery in newborns.[2, 3] However, cultures in those two cases were obtained by expressing pus from the Stensen's duct, which can lead to contamination of the specimens by the oral flora.

This report describes two newborns with suppurative parotitis caused by anaerobic bacteria.

Patient 1. A 22-day-old male infant presented with swelling of the right parotid gland of 4 days duration. The newborn was delivered by uncomplicated vaginal delivery at 36 weeks of gestation and his birth weight was 3200 g. He was hypotonic and sluggish at the age of 4 h. He manifested hyperbilirubinemia and required exchange transfusion on the third day. He was treated with ampicillin and gentamicin for 5 days and improved within 48 h. The child was discharged at the age of 11 days. On admission his weight was 3550 g, and the total white blood cell count was 14 400/mm^3 with 72% neutrophils, 20% lymphocytes and 8% monocytes. Two-blood culture were sterile. He manifested fever of 38.6°F, erythema and fluctuant swelling of the right parotid gland, and purulent exudate was exuding from the Stensen's duct when pressure was applied to the gland. The parotid gland was aspirated through the skin above the gland (after skin disinfection), and the material was sent for Gram stain and cultures for aerobic and anaerobic bacteria. Surgical drainage was performed, and 6 ml of foul smelling purulent material was obtained. A Gram-stained smear showed numerous WBC and Gram-positive cocci in chains and Gram-negative bacilli. Cultures for anaerobic bacteria yielded heavy growth of *Peptostreptococcus intermedius* and *Prevotella melaninogenica*. The *P. melaninogenica* produced beta-lactamase. The patient was treated with 5 mg/kg intravenous clindamycin every 6 h for 2 weeks, followed by oral clindamycin, 7.5 mg/kg every 6 h for 1 week. The swelling resolved within 2 weeks, and the patient was discharged with complete recovery.

Patient 2. An 18-day-old female infant presented with swelling of the left parotid gland of 5 days duration. She was delivered by uncomplicated vaginal delivery at 40 weeks of gestation, and her birth weight was 3500 g. She manifested physiologic hyperbilirubinemia at the age of 2 days. The child was discharged at the age of 4 days. On admission her weight was 4050 g, and the total white blood cell count was 18 200/mm^3 with 68% neutrophils, 24 lymphocytes and 8 monocytes. Two-blood cultures were sterile. She had erythema and fluctuance of the left parotid gland, and purulent exudate was exuding from the Stensen's duct when pressure was applied to the gland. The parotid gland was aspirated through the skin above the gland (after skin disinfection), and the material was sent for Gram stain and cultures for aerobic and anaerobic bacteria. Surgical drainage was performed and 8 ml of foul smelling purulent material was obtained. Gram-stained smear showed numerous white blood cells and Gram-negative bacilli. Cultures for anaerobic bacteria yielded heavy growth of *Prevotella intermedia*. The organism produced beta-lactamase. Treatment was with ticarcillin-clavulanate 75 mg/kg every 6 h for 10 days followed by amoxicillin/clavulanate 15 mg/kg every 8 h for 11 days. The swelling resolved within 10 days, and the patient was discharged with complete recovery.

Discussion. This report describes for the first time the isolation of anaerobic bacteria from two newborns with suppurative parotitis. The organisms were recovered from specimens obtained through aspiration of the infected gland, thus avoiding contamination of the material by the normal oral bacterial flora. The lack of their recovery in most previous reports may be a result of the use of improper methods for their collection, transportation and cultivation.[1, 4]

The isolation of anaerobic bacteria is not surprising because these bacteria are the predominant organisms in the oropharynx where they outnumber aerobes in the ratio of 10:1 to 100:1 in the neonate[8] and are important pathogens in other suppurative infections in and around the oropharynx.[5] *Prevotella* species are the most common anaerobic Gram-negative bacilli found in oral flora and, like *Peptostreptococcus* species, are frequently isolated from odontogenic orofacial infections.[5]

The resistance of *S. aureus* and the *Bacteroides fragilis* group to penicillin has been recognized for more than two decades. However, in recent years a growing number of anaerobic Gram-negative bacilli produce this enzyme.[5]

The administration of antimicrobial therapy is an essential part of the management of patients with suppurative parotitis. The choice of antibiotics depends on the etiologic agent. Most cases respond to medical management; however, sometimes an inflamed gland may reach a stage of abscess formation that requires surgical drainage. Empiric therapy with anti-staphylococcal therapy with beta-lactam resistant peni-

cillin is indicated in all cases. Coverage may also be necessary for hemolytic streptococci and anaerobic bacteria.

A penicillinase resistance penicillin or a first generation cephalosporin is generally adequate coverage for *S. aureus*. However, the pressure of methicillin-resistant staphylococci may mandate the use of vancomycin. Clindamycin, cefoxitin, imipenem, the combination of metronidazole and a macrolide or a penicillin plus a beta-lactamase inhibitor provide adequate coverage for anaerobic as well as aerobic bacteria.

Itzhak Brook, M.D., M.Sc.
Department of Pediatrics
Georgetown University School of Medicine
Washington, DC

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Address for reprints: Itzhak Brook, M.D., M.Sc., PO Box 70412, Chevy Chase, MD 20813-0412. Fax 301-295-6503; E-mail IB6@GEORGETOWN.EDU.

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OPHTHALMOMYIASIS IN A CHILD

A 4-year-old child presented with a 3-week history of left eye swelling. The periorbital inflammation was a result of a larva of the human botfly, *Dermatobia hominis*. Surgical extraction of the larva was curative.

Periorbital swelling is common in children. It may result from trauma, infection, allergy or, rarely, tumor. Periorbital cellulitis, orbital cellulitis and dacrocystitis are the leading infectious causes of periorbital swelling and may be difficult to distinguish.[1] Bacteria often associated with periorbital infections include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, group A streptococci and *Staphylococcus aureus*.[2] Other infectious agents such as parasites can also cause periorbital swelling but are much less common.[3] The present report describes a young child who presented with clinical "periorbital cellulitis" resulting from infestation with the larva of a human botfly.

Case. AK was a 4-year-old boy with a 2-week history of swollen, red, left upper and lower eyelids. The parents initially noticed several insect bites around the left eye, approximately 1 week before the eye became erythematous and swollen. One week later his pediatrician prescribed amoxicillin/clavulanate for presumed cellulitis. He remained afebrile. After 7 days of treatment and no improvement, he was admitted to the hospital.

On examination AK was comfortable and had no complaints. The left eyelid was swollen and erythematous. Three papules were seen, two on the lateral lower lid and one on the nasal aspect of the upper lid. The latter had scant clear discharge. The area involved was not tender. The globe was not proptotic, and extraocular movements were intact.

Laboratory tests demonstrated a white blood cell count of 8400/mm^3. A Gram-stained smear of the draining papule showed no bacteria, and the culture was negative. A computerized axial tomographic study demonstrated preseptal swelling and normal postseptal anatomy.

He was treated with oxacillin, 150 mg/kg/day, intravenously for a presumed preseptal cellulitis. The swelling lessened during the next 2 to 3 days; however, the upper medial aspect of his left eye continued to be inflamed. Close examination disclosed a white, shiny foreign body moving within the papule on the upper lid (Fig. 1). The child was taken to the operating room where a 0.7-cm larva was extracted and identified as the human botfly, *Dermatobia hominis* (Fig. 2). Two days later the lid swelling and erythema resolved. The child was discharged on dicloxacillin, 20 mg/kg/day orally, to complete 10 days of antibiotic treatment for a possible secondary infection. No cultures were obtained at the time of surgery. He was also treated with topical antibiotic ointment.

Discussion. Myiasis is the invasion of human tissue by *Diptera* larvae. Ophthalmomyiasis is the invasion of the lid, conjunctiva, cornea, orbit or the globe and represents 5% of all cases of myiasis.[4] The most common cause of ophthalmomyiasis is the sheep botfly, *Oestrus ovis. D. hominis*, the etiology in our patient, is less common.[5]

To initiate human infection, the female botfly first attaches her eggs to an insect such as a mosquito. When the mosquito lands on a human and deposits the egg, the warmth of the skin causes the eggs to hatch. Within minutes the larva penetrates the skin, usually through the bite of the mosquito or along a hair follicle.[3, 5] The presence of the larva within the skin incites a local inflammatory reaction. Patients infested

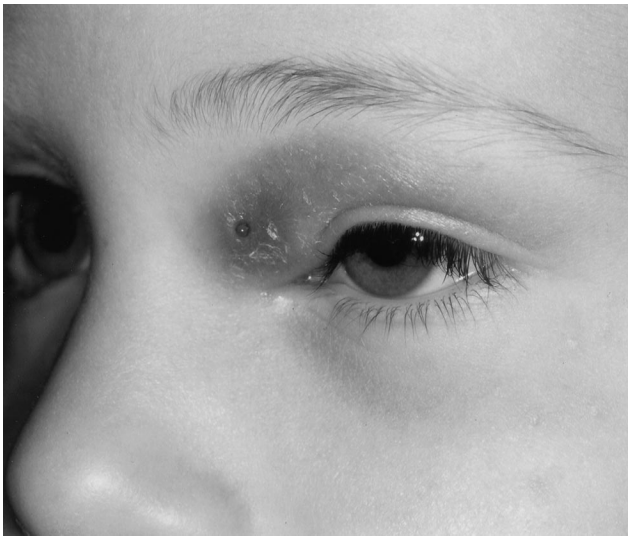

FIG. 1. Periorbital inflammation. Small opening with larva visible.

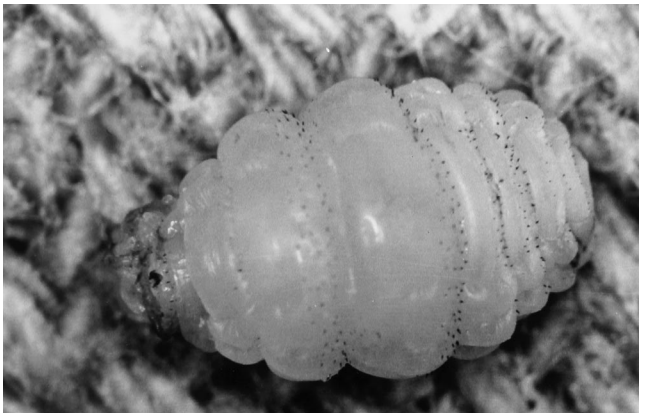

FIG. 2. Larva of *D. hominis*.

with a larva often complain of pruritis and pain, and they may sense movement of the larva. Extraction of the larva is difficult because rows of small spicules on the organism attach to subcutaneous tissues (Fig. 2). Surgical incision facilitates removal of the larva and is the preferred management.

Mary E. Emborsky, D.O.
Howard Faden, M.D.
State University of New York School of Medicine and Biomedical Sciences at Buffalo and the Children's Hospital of Buffalo
Buffalo, NY

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IS NOMA NEONATORUM A PRESENTATION OF ECTHYMA GANGRENOSUM IN THE NEWBORN?

Noma neonatorum was suggested as a distinct entity characterized by a gangrenous process of the nose, oral cavity, eyelids and perineum that was almost universally fatal in premature infants with *Pseudomonas* sepsis. We report the first case of noma neonatorum in a 26-week-gestation twin born in the United States. Our case is consistent with previous descriptions of noma neonatorum; however, we question the distinction between noma neonatorum and a neonatal presentation of ecthyma gangrenosum.

In 1978 Ghosal et al.[1] reported a series of 35 premature and low birth weight newborn infants (6 to 23 days of age) with a gangrenous process of the nose, eyelids, oral cavity, anal region and genitalia that they designated noma neonatorum. *Pseudomonas aeruginosa* was isolated from the majority of skin lesions (96%), and 86% of them also had *Pseudomonas* sepsis with positive blood cultures. The outcome was almost uniformly fatal. The name noma neonatorum was suggested because of the similarity of the histopathologic findings to noma, a disease of young, often debilitated children characterized by gangrenous sloughing of tissue in the oronasal region.[2] Although these entities are histologically similar and both predominate in developing countries, the etiologic agents differ (i.e. *Pseudomonas* in noma neonatorum and mainly *Fusobacterium* in noma). We report a case of a premature infant with noma neonatorum and review the literature, which we interpret as indicating that noma neonatorum represents ecthyma gangrenosum in newborns.

Case report. The patient is a female twin delivered at 26 weeks gestation. The pregnancy was complicated by premature labor, and the mother had received perinatal steroids and antibiotics. The baby was delivered by cesarean section with rupture of membranes at delivery. Apgar scores were 6-7-7 at 1-5-10 min, and the weight was 808 g. The baby was intubated at 1 min of life for respiratory distress. The initial complete blood count (CBC) showed a white blood cell count of 2000/μl with 26% neutrophils, 57% lymphocytes and 17% monocytes; hemoglobin of 17.9 g/dl (normal range, 11.0 to 15.8 g/dl); and platelets of 215 000/μl. A blood culture was taken, and the baby was treated with ampicillin and gentamicin until 72 h of age when all cultures were reported to be negative. During the first 2 weeks she had respiratory distress syndrome, hyperbilirubinemia and serum glucose instability. On Day 14 she developed increasing respiratory distress associated with lethargy and mottling of her skin. A sepsis evaluation was performed including blood and endotracheal cultures, and a CBC had a hemoglobin of 11.2 g/dl, platelets of 293 000/μl and a white blood cell count of 8100/μl with 12% segmented neutrophils, 5% band forms, 21% lymphocytes, 10% monocytes, 1% eosinophils and 3% metamyelocytes. She was treated empirically with vancomycin, ampicillin and gentamicin. On Day 15 a pustular rash appeared in the groin and perianal regions. In addition she developed hemodynamic instability necessitating pressor support with dopamine. The following day the sputum and pustular lesion cultures grew *P. aeruginosa,* and the antibiotic regimen was changed to ceftazidime, tobramycin and ampicillin. Treatment was later changed to intravenous meropenem and tobramycin based on antibiotic susceptibility test results, and topical silver sulfadiazine was applied to the skin lesions. The blood cultures remained negative.

Physical examination on Day 17 revealed an afebrile premature infant with stable vital signs while receiving dopamine. Her skin was mottled and necrotic ulcers were evident in the right labia majora and in the perianal region. The perianal region was also erythematous and edematous around the necrotic center. In addition the left lateral portion of the upper lip had full thickness tissue necrosis with sloughing, which had previously been obscured by the endotracheal tube tape. The rest of the physical examination was unremarkable. A repeat CBC showed a hemoglobin of 11.4 g/dl, platelets of 91 000/μl and white blood cell count of 14 000/μl with 9% segmented neutrophils, 32% band forms, 22% lymphocytes, 23% monocytes, 7% eosinophils, 4% atypical lymphocytes, 2% metamyelocytes and 1% myelocytes. The dermatology service was consulted and the diagnosis of ec-

thyma gangrenosum was suggested. Continuation of the current antibiotic regimen was recommended.

During the ensuing several days the patient showed definite improvement. She was quickly weaned off the dopamine, the ventilator settings were reduced and her activity improved. The necrotic areas of the labia majora, upper lip and perianal region sloughed, leaving healthy appearing granulation tissue beneath. The remainder of her nursery course was complicated by bronchopulmonary dysplasia and central intravenous catheter sepsis with a coagulase-negative staphylococcal isolate. She was discharged on Day of Life 90 solely on medications for gastroesophageal reflux. Her twin brother had *P. aeruginosa* sepsis several days after her *Pseudomonas* illness started. Although he had positive blood cultures, he never developed skin lesions and had a full recovery. The mother had remained well, without fever or other signs of infection.

Discussion. Noma neonatorum is a distinct entity from noma because it occurs in the first month of life in newborns who are debilitated from prematurity or other illnesses. In the original series of 35 patients, the lesions were seen in the majority of cases in the orofacial region (27 of 35 patients), as well as in the anogenital region in 7 of 35 patients.[1] The histopathology of the lesions shows necrosis originating in the perivascular regions of the subcutaneous tissue and extending superficially into the dermis. The epidermis is necrosed when the papillary layer of the dermis is involved. There is loss of elastic tissues, and in a few cases an acute inflammatory reaction was noted. This histopathology is similar to noma, which also shows perivascular necrosis and inflammation in the subcutaneous tissues underlying mucous membranes.[2] In the original series noma neonatorum was almost uniformly fatal.[1]

Since the first suggestion of noma neonatorum as a nosologic entity, there have been reports of at least seven patients with involvement of the oral cavity, nose and perineum.[3–8] All patients had positive cultures from the lesions for *Pseudomonas*, and several also had positive blood cultures. Three of the seven reported patients died from overwhelming *Pseudomonas* sepsis. Investigation for immunologic deficiencies was not reported in most of the patients, although in one case (a full term infant with choanal atresia), neutropenia and B cell deficiency were present during the acute illness.[3] After the infant recovered, these abnormalities disappeared. The majority of the patients described with noma neonatorum were born in developing countries (i.e. India, China, Lebanon and Israel).[3–8] Although Eisele et al.[2] reported a case seen in the US, this patient had been born in Calcutta, India. Our patient is the first reported patient with noma neonatorum born in the United States.

It is interesting to ponder whether noma neonatorum is a distinct entity from ecthyma gangrenosum in the newborn. Ecthyma gangrenosum describes skin lesions often associated with *P. aeruginosa* sepsis in patients who are immunologically compromised.[9–13] These skin lesions are present in ~3 to 6% of patients with *Pseudomonas* bacteremia. The lesions start as red macules that progress to hemorrhagic bullae or necrotic vesicles and eventually to necrotic ulcers with eschar formation.[12] Pathology reveals inflammation and necrosis in the perivascular regions in the dermis and subcutaneous tissues.[9, 11] The lesions occur predominantly in the perineal area and the extremities; facial involvement is rare.[11] The mortality with ecthyma gangrenosum is high (in one series, 50%).[11] The similarities to noma neonatorum include the etiologic agent (*Pseudomonas*), the progression of the skin lesions to necrotic ulcers, the occurrence in debilitated patients and the high mortality. The main distinctions between ecthyma gangrenosum and noma neonatorum traditionally have been the age at diagnosis and the location of the lesions. Ecthyma gangrenosum has been only occasionally reported in infancy.[14–16] One review of 21 very low birth weight infants with *Pseudomonas* sepsis at a large hospital did not include any infants with skin lesions.[17] However, ecthyma gangrenosum has been diagnosed in neonates and noma neonatorum in infants beyond the immediate neonatal period.[6, 10, 18, 19] Therefore the line of distinction between noma neonatorum and ecthyma gangrenosum does not seem clear.

We describe a premature infant with a presentation consistent with noma neonatorum. However, from our review of the literature it seems there is no clear difference between noma neonatorum and ecthyma gangrenosum, and we suggest that noma neonatorum represents a neonatal form of ecthyma gangrenosum. Several investigators suggested that the two are distinguished somewhat by the location of lesions (with noma neonatorum showing a predominance of facial lesions), the age of presentation and the underlying condition. However, the etiologic agent in almost all of the cases is the same (*P. aeruginosa*) and the histopathology similar. In addition premature babies are considered immunosuppressed and would thus be more susceptible to ecthyma gangrenosum.

Alexandra F. Freeman, M.D.
Anthony J. Mancini, M.D.
Ram Yogev, M.D.
Pediatric Infectious Disease (AFF, RG) and Pediatric Dermatology (AJM) Divisions
Children's Memorial Hospital
Northwestern University Medical School
Chicago, IL

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Key words: Noma neonatorum, ecthyma gangrenosum, neonatal infection, *Pseudomonas*.

Address for reprints: Alexandra Freeman, M.D., Department of Infectious Diseases, Children's Memorial Hospital, 2300 Children's Plaza, Chicago, IL 60614. Fax 773-880-8226; E-mail afreeman@childrensmemorial.org.

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DENOUEMENT—*CONTINUED FROM P. 75*

Motile amebas were identified on wet mount of the cerebrospinal fluid (CSF) obtained by lumbar puncture on the day before the patient's death. Serum obtained 5 days before the patient's death had a positive *Balamuthia mandrillaris* titer of 1/512. This test was performed by indirect immunofluorescence by Carol Glaser, D.V.M., M.D. and Fred Schuster, Ph.D. from the Viral and Rickettsial Disease Branch of the State of California Department of Health Services. Autopsy of the brain revealed massive necrosis of gray and white matter and the presence of amebic trophozoites, particularly around the fourth ventricle and brain stem. The amebas were clustered around vessels. The meninges were thickened. No amebas were found in any other organ. Direct immunofluorescence on brain tissue sections, which was performed by Govinda Visvesvara, Ph.D. at the Division of Parasitic Diseases at the Centers for Disease Control and Prevention, confirmed the presence of *B. mandrillaris,* and the organism subsequently grew on cultures inoculated with the patient's spinal fluid at the State of California Department of Health Services.

B. mandrillaris is a newly recognized free-living ameba, which has been reported to cause meningoencephalitis in immunocompetent and immunocompromised humans and animals. Amebic meningoencephalitis is classically divided in two clinical entities. (1) Primary amebic meningoencephalitis, which is usually caused by *Naegleria* species, is an acute, fulminant disease leading to death within a few weeks in almost all cases. Primary amebic meningoencephalitis occurs in healthy children or young adults who have a history of swimming in freshwater lakes during the week before onset of illness. Transmission occurs through introduction of water containing *Naegleria* into the nasal cavities and direct invasion of the central nervous system through the olfactory apparatus.[1] (2) Granulomatous amebic encephalitis is usually caused by *Acanthamoeba* species and occurs in chronically ill or immunosuppressed patients, without any exposure history to contaminated water. The onset of granulomatous amebic encephalitis is insidious and the patients present with focal neurologic deficits. Suggested portals of entry are lungs, skin and genitourinary tract, followed by hematogenous spread and seeding of various tissues including the central nervous system. The clinical course is subacute to chronic and leads to death within weeks to several months.[1]

B. mandrillaris was previously referred to as leptomyxid amebas, a group of innocuous soil organisms. The first documented case of central nervous system infection caused by *B. mandrillaris* occurred in a mandrill that died of meningoencephalitis at the San Diego Zoo in 1990.[2] In 1991 a case of granulomatous meningoencephalitis secondary to *B. mandrillaris* was described in a patient with AIDS.[3] Over the recent years several cases of meningoencephalitis secondary to *B. mandrillaris* have been reported in immunocompetent and immunocompromised children and adults, and several cases of granulomatous amebic encephalitis, which had previously been attributed to *Acanthamoeba* infection were retrospectively proven to have been caused by *B. mandrillaris*.[4–7] As of January, 1997, 63 cases of *B. mandrillaris* infection in humans and animals have been reported globally.[4] The pathogenesis and route of infection with *B. mandrillaris* are unknown. Case reports of patients with multiple foci of infection suggest hematogenous dissemination, but the portal of entry is unknown.

Most patients with *B. mandrillaris* meningoencephalitis present with focal neurologic findings and seizures.[3–8] There does not seem to be any particular age predilection, because age of the described patients ranges from a few months to >70 years.[7] Some of the patients are febrile at the time of presentation.[3–7, 9] Peripheral complete blood counts are usually within normal limits.[4, 5, 7] In most cases CSF findings are significant for pleocytosis up to 500 white blood cells/mm^3 with lymphocytic and monocytic predominance. CSF protein is usually mildly to moderately elevated but can be highly elevated (1 to 2 g/dl), and glucose can be normal or decreased; even undetectable glucose values have been described.[7, 8] Radiographic imaging might show focal enhancing lesions, cystic lesions, diffuse brain edema, hydrocephalus and lesions compatible with stroke.[3–9] Biopsy or autopsy show hemorrhagic necrosis of the brain with amebic trophozoites and cysts and inflammatory infiltrate with lymphocytes and monocytes. There are clusters of amebas and inflammatory cells around blood vessels. True granulomas have not been described.[2–9]

There are no reported survivors, and the diagnosis is usually made on postmortem examination. To our knowledge this is the first case of detection of motile amebas on wet mount of spinal fluid in a patient with *B. mandrillaris* meningoencephalitis. There is no known effective therapy for *B. mandrillaris* infection. *In vitro* testing of pentamidine isethionate seemed to be the most effective. The drug inhibited amebic growth by 93% after 6 days of exposure but was not amebicidal. Fluconazole and ketoconazole had some inhibitory effect on amebic growth; amphotericin B was marginal in its effects. Azithromycin, clarithromycin and trimethoprim-sulfamethoxazole had no effect on amebic growth.[10]

Amebic encephalitis should be considered in the differential diagnosis of undiagnosed meningoencephalitis with very high protein and low glucose concentrations in the CSF. Wet mount examination of the CSF should be obtained for demonstration of the parasite.

Key words: Ameba, encephalitis, amebic meningoencephalitis, *Balamuthia mandrillaris* encephalitis.

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Current Abstracts

EDITED BY ROBERT J. LEGGIADRO, M.D.

INTRAABDOMINAL INFECTION DUE TO *STREPTOCOCCUS PNEUMONIAE.* D. Dugi III et al. *Medicine 2001; 80:236–44.*

The authors report five new cases and review the literature on intraabdominal infection caused by *Streptococcus pneumoniae.* The more common form of this infection is peritonitis, which occurs as a complication of a preexisting peritoneal abnormality, e.g. ascites, or *de novo* (spontaneous or primary) in an otherwise healthy individual. Less common is infection of, or adjacent to, an organ of the digestive tract, e.g. peritonitis caused by a perforated gastric ulcer or appendiceal abscess.

Fifty-nine (77%) of 77 reported cases of primary pneumococcal peritonitis in patients with prior peritoneal disease and age noted were children. The underlying disease of 42 (71%) of the 59 children was nephrotic syndrome. Sixteen (27%) children had liver disease and 1 was on chronic peritoneal dialysis. All 36 cases of primary pneumococcal peritonitis in patients with no prior peritoneal disease reported since 1950 were female. Nine (25%) of 36 with age noted were children. Appendicitis (4) and enteritis (1) were the clinical findings in 5 children of 32 patients reported with pneumococcal infection of, or adjacent to, an intraabdominal organ.

Comment: In the preantibiotic era most cases of pneumococcal peritonitis were attributed to bacteremia from pneumonia. Currently primary peritonitis as a complication of preexisting ascites is believed to result from organisms reaching the peritoneal cavity by translocation from the bowel. It is likely that organisms reach the peritoneal cavity by migration via the female genital tract in peritonitis in the absence of prior peritoneal disease, which almost always occurs in female patients. The presence of an intrauterine device or a recent vaginal delivery may facilitate pneumococcal migration to the peritoneum in such cases.

MOLECULAR BASIS FOR HIGH VIRULENCE OF HONG KONG H5N1 INFLUENZA A VIRUSES. M. Hatta et al. *Science 2001;293:1840–2.*

In 1997 an H5N1 influenza A virus was transmitted from birds to humans in Hong Kong, killing 6 of the 18 people infected. When mice were infected with the human isolates, two virulence groups became apparent. The authors used reverse genetics to demonstrate that a mutation at position 627 in the PB2 protein influenced the outcome of infection in mice. An H5N1 isolate that was highly lethal for mice was markedly attenuated by a Lys-to-Glu substitution at this position; on the other hand, a Glu-to-Lys substitution at this position converted an isolate that did not cause severe disease in mice into one that caused multiorgan, lethal disease. Moreover the virulence of H5N1 isolates depended on high cleavability of the hemagglutinin glycoprotein. These results suggest that virulence of H5N1 influenza isolates in mice, and possibly in humans, involves hemagglutinin cleavability and an amino acid substitution in position 627 of the *PB2* gene.

Comment by Steve Buckingham, M.D., Memphis, TN: When persons of all ages are considered, influenza viruses are the most important infectious causes of respiratory morbidity and mortality worldwide. The 20th century was marked by three influenza pandemics (in 1918, 1957 and 1968), each of which caused widespread illness and death. It is possible that a fourth pandemic in 1997 was narrowly averted by the slaughter of all chickens in Hong Kong after the recognition of the first cases of H5N1 disease in humans. Now, with the use of modern reverse genetic techniques, we begin to gain some insight into why the 1997 H5N1 isolates were so highly pathogenic (33% mortality) in humans. It is disquieting that, at least in mice, a single amino acid substitution can turn a relatively avirulent strain of influenza into a highly lethal virus. Given that live bird markets in southern China provide an ideal arena of exchange of genetic material between influenza A viruses, it appears inevitable that novel strains of influenza will continue to emerge and possibly threaten the health of humans around the world.