Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Nasopharyngeal viral isolates in children with Haemophilus influenzae type B meningitis

Sheldon L. Kaplan, M.D.,* Larry H. Taber, M.D., Arthur L. Frank, M.D., and Ralph D. Feigin, M.D.,
Houston, Texas

Viruses have been implicated in the pathogenesis of certain bacterial infections. Influenza and parainfluenza viruses potentiate the action of Haemophilus influenzae type b in experimental animals. In the infant rat model, prior inoculation with influenza virus decreased by 100-fold the dose of H. influenzae type b required to produce meningitis in rats without prior viral inoculation.

Symptoms and signs consistent with preceding upper respiratory tract infection frequently are present in children with bacterial meningitis. We report the results of nasal wash viral cultures in a group of children with meningitis caused by H. influenzae type b.

MATERIALS AND METHODS

Fifty-three children hospitalized at Texas Children's Hospital (40) and Ben Taub General Hospital (13) with H. influenzae meningitis were enrolled in this study between February 13, 1979, and March 20, 1980, after signed informed parental consent was obtained. The ages of the children ranged between 42 days and 5 1/2 years. Parents were questioned about the presence of symptoms of the upper respiratory tract (rhinorrhea, cough, sore throat, congestion, etc.) in their children prior to admission. H. influenzae type b was isolated and identified by standard techniques in the pathology laboratories.

Nasal wash specimens for viral culture were obtained within 24 hours of admission and were inoculated onto human embryonic kidney, HEP-2, Rhesus monkey kidney, and WI-38 tissue cultures. Viral isolates were identified by cytopathic effects and indirect immunofluorescent techniques.

Children in the Houston Family Study served as a community comparison group. They had nasal wash viral cultures and a physical examination whenever upper respiratory symptoms occurred. Viral cultures from the same age group and time period as for the patients with meningitis were included in this study. Methods were the same as for the patients with meningitis except that tissue cultures used were HEP-2, WI-38, LLC-MK2, and MDCK.

RESULTS

A virus was isolated from nasal wash specimens obtained at the time of admission from 12 (22.6%) of 53 children with meningitis caused by H. influenzae type b. In the community comparison group with upper respiratory signs and symptoms during the same period, 193 (14.5%) of 1,329 cultures obtained were positive for virus. The specific agents recovered are shown in the Table.

Seventy-four percent of children with H. influenzae type b meningitis had symptoms of upper respiratory tract disease prior to admission. Eighty percent of those with positive viral cultures and 71% of those with negative viral
Table. Results of virus cultures of nasal washes from children with *Haemophilus influenzae* type b meningitis or upper respiratory illness, February, 1979, to March, 1980, Houston, Texas

| Culture result | Meningitis | Upper respiratory illness* |
|----------------|------------|----------------------------|
| Picornaviruses |            |                            |
| Unclassified† | 1          | 62                         |
| Rhinovirus     | 6          | 32                         |
| Enterovirus    | 3          | 26‡                        |
| Poliovirus     | 0          | 3                          |
| Parainfluenza 2| 1          | 2                          |
| Parainfluenza 1 and 3 | 0 | 38                         |
| Adenovirus     | 1          | 11                         |
| Respiratory syncytial virus | 0 | 9                          |
| Other          | 0          | 8                          |
| Negative       | 41         | 1,136                      |

*Only uncomplicated upper respiratory infection included. Illnesses with pharyngitis, otitis media, or lower respiratory signs or symptoms were excluded.

†Not further classified as rhinovirus, enterovirus, or poliovirus at this time.

‡Of 18 tested, no polioviruses identified.

cultures had a history of upper respiratory tract illness prior to admission.

**DISCUSSION**

*Haemophilus influenzae* type b meningitis is thought to follow hematogenous dissemination of the organism to the central nervous system after a period of residence of the organism in the nasopharynx. The factors which allow *H. influenzae* type b to enter the bloodstream from the respiratory tract are unknown, but absence of antibody directed against the polyribosephosphate capsule may play a role.

In animal models, viruses can be shown to influence the evolution of bacterial infections. Francis and DeTorregrosa demonstrated that the majority of mice that had received influenza virus intranasally one to four days prior to the intranasal administration of *H. influenzae* type b developed pneumonia and died. In contrast, those receiving only *H. influenzae* did not die and those receiving only influenza virus died occasionally. Degre and Glasgow noted a similar synergistic effect of sequential administration of parainfluenza 1 and *H. influenzae* type b in mice.

Michaels and co-workers studied the effect of prior inoculation of influenza A virus (A/Port Chambers) 74 strain (H3N2) upon the development of *H. influenzae* type b meningitis in infant rats. When the animals first were infected with influenza A virus, the number of bacteria necessary to produce meningitis was reduced 100-fold. In a preliminary report, Krasinski and Nelson observed that influenza A, parainfluenza 1 and 2, and respiratory syncytial virus significantly increased the susceptibility of infant rats to *H. influenzae* type b bacteremia and meningitis. The mechanisms by which viral agents act to promote bacterial infections in these animal models are unknown; the virulence of the organism may be enhanced or host resistance may be decreased.

In man, prior viral infection has been associated with the development of central nervous system infections. Levitt et al reported an outbreak of meningococcal and ECHO-9 meningitis occurring simultaneously; in three patients there was evidence to suggest dual viral and bacterial infection. Young et al described a concurrent outbreak of influenza A2 and *Neisseria meningitidis* infections in an enclosed population.

In our study, 75% of children with *H. influenzae* type b meningitis had a history consistent with a viral upper respiratory infection prior to admission. The association based on parental history was supported by the frequency of viral isolation from the nasal secretions; the rate was as high in the patients with meningitis as in the comparable group of children sampled because of upper respiratory illness. Although the numbers are small, the data suggest that the viruses associated with the history of recent upper respiratory illness in meningitis may be those that cause year-round, mild disease and are often difficult to isolate. The virus isolation rate for year-round upper respiratory illness was also low in the community group during this period. Few surveys of mild illness are available for comparison of isolation rates.

We observed an association between *H. influenzae* type b meningitis and preceding upper respiratory illness probably due to viral agents. In view of previous animal studies, this finding is suggestive of a pathophysiologic relationship.

**REFERENCES**

1. Francis T, and DeTorregrosa MV: Combined infection of mice with *H. influenzae* and influenza virus by the intranasal route, J Infect Dis 76:70, 1945.
2. Gerone PJ, Ward TG, and Chappell WA: Combined infections in mice with influenza virus and *Diplococcus pneumoniae*, Am J Hyg 66:331, 1957.
3. Buddingh GJ, Al-Talib AM, and Pipes FJ: Combined viral and bacterial infection. An in vitro analysis of the population dynamics and factors influencing the enhancement of virulence of *Haemophilus influenzae* in combined infection with influenza virus in embryonated eggs, Am J Pathol 49:353, 1966.
4. Degre M, and Glasgow LA: Synergistic effect in viral bacterial infection. I. Combined infection of the respiratory tract in mice with parainfluenza virus and *Haemophilus influenzae*, J Infect Dis 118:449, 1968.
5. Michaels RH, Myerowitz RL, and Klaw R: Potentiation of
APPROXIMATELY 500 to 1,000 nocardial infections are estimated to occur in the United States each year. * Nocardia* usually causes opportunistic infections in the compromised host; however, infection may occur in patients without a predisposing condition. Most childhood infections are pulmonary or systemic; skin or subcutaneous infections are infrequently reported.  

Recently, we have evaluated three children with cervicofacial nocardiosis. Their cases are summarized here to emphasize the unique clinical presentation, ease of diagnosis, and prompt response to appropriate therapy of this form of nocardiosis, as well as the lack of association with any immune deficiency.

**CASE REPORT**

Patient 1, a 22-month-old Caucasian girl, was hospitalized because of a pustular facial lesion and swelling in the left submandibular area. Two weeks before admission she received amoxicillin for ten days orally for a draining ear. The ear drainage ceased and two days before admission she developed a erythematous papule on his left cheek. Five days later he was given cephalexin orally after the lesion was cultured. The pustule beneath the left naris increased in size and the patient received erythromycin orally; however, the pustule increased in size and the patient gave up treatment, she was hospitalized. A Gram stain was performed after three days. After 72 hours of incubation on the blood agar plate, *Nocardia brasiliensis* was isolated from the patient. The skin lesion on the cheek was reported as having no growth on blood agar. The patient received trimethoprim/sulfamethoxazole orally with resolution of the pustule and lymphadenopathy. Quantitative immunoglobulin values were within the normal range.

Patient 2, a 5-year-old Caucasian boy, first developed an erythematous papule on his left cheek. Five days later he was given cephalaxin orally after the lesion was cultured. The following day methicillin was given intramuscularly, but he developed a 3 × 3 cm tender left submandibular node and fever, and was hospitalized and given methicillin intravenously. His lymphadenopathy increased despite therapy. The culture of the pustule was reported as having no growth on blood agar after 48 hours. The patient was treated with trimethoprim/sulfamethoxazole orally with resolution of the pustule and lymphadenopathy. Quantitative immunoglobulin values were within the normal range.

Patient 3, a 3-year-old Oriental girl, developed progressive swelling in the left submandibular area followed by a small draining pustule on the left naris. The following day she developed fever and was treated with penicillin. Because there was no response to treatment, she was hospitalized. A Gram stain was performed after three days. After 72 hours of incubation on the blood agar plate, *Nocardia brasiliensis* was isolated from the patient. The skin lesion on the cheek was reported as having no growth on blood agar. The patient received trimethoprim/sulfamethoxazole by mouth for four weeks and the submandibular lymph node, which prompted admission. Initially the patient was treated with metronidazole parenterally, but the pustule and lymphadenopathy worsened and an incision and drainage was performed after three days. After 72 hours of incubation on the blood agar plate, *Nocardia brasiliensis* was isolated from the small amount of purulent material obtained at surgery. A culture of the pustule was reported as having no growth on blood agar after 48 hours. The patient was treated with trimethoprim/sulfamethoxazole orally with resolution of the pustule and lymphadenopathy. Quantitative immunoglobulin values were within the normal range.

**Cervicofacial nocardiosis in children**

Richard M. Lampe, M.D., LTC, MC, USA,* Carol J. Baker,** M.D., Edward J. Septimus, M.D., and Richard J. Wallace, Jr., M.D., Houston, Texas

From the Department of Pediatrics, Section of Infectious Diseases, Departments of Medicine, Microbiology and Immunology, Baylor College of Medicine.

*Reprint address: Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030.

**Recipient of Research Career Development Award 1 KO4 AI 00326 from the National Institute of Allergy and Infectious Diseases.