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INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

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Interests:

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Bacterial Meningitis

The modern era in the treatment of bacterial meningitis began with the 1949 report by Dowling et al., that high dose penicillin reduced the case fatality rate in pneumococcal meningitis from being usually fatal to 30 percent. From 1949 through the 1960s, the overwhelming majority of bacterial of causes of bacterial meningitis admitted to a medical service would have been cased by *Streptococcus pneumoniae* and *Neisseria meningitidis*. The consensus was that in adult bacterial meningitis, empiric treatment could be with penicillin alone. Developments occurred which limited the generalization. *Haemophilus influenzae* was determined to be a pathogen in adult meningitis and 15 percent of isolates were ampicillin resistant. L*isteria monocytogenes* and gram negative bacteria other than *Haemophilus influenzae* also were determined to be pathogens that could cause adult meningitis. The etiologies of bacterial meningitis on the medical service at Parkland Memorial Hospital during the 1980s and 1990s are compared (Table 1). In the 1980s, 100 episodes in 98 patients were studied and in the 1990s, 92 episodes in 90 patients were analyzed. During both decades, *Streptococcus pneumoniae* was the most common pathogen accounting for 53 – 56 percent of cases.

Table 1
Etiology of Bacterial Meningitis on the Medical Service

	1980s*	1990s**
S. pneumoniae	56	49 (53.3)
N. meningitidis	16	14 (15.2)
L. monocytogenes	7	4 (4.4)
S. aureus	5	6 (6.5)
H. influenzae	5	4 (4.4)
Streptococci		
Group A		1 (1.1)
Group B	1	7 (7.6)
Enterococcus	2	1 (1.1)
Group D (non-enterococcus)		1 (1.1)
viridans streptococcus	1	1 (1.1)
Gram negative bacteria		
E. coli	4	2 (2.2)
E. cloacae		1 (1.1)
K. pneumoniae	1	
Ps. aeruginosa	1	1 (1.1)

*100 episodes in 98 patients No.=%
**92 episodes in 90 patients No. (%)

Neisseria meningitidis was the second most common pathogen accounting for 15 – 16 percent of cases. *Listeria monocytogenes* was the third most common pathogen accounting from 4 – 8 percent of cases. *Staphylococcus aureus* was the next most common pathogen accounting from between 5 – 7 percent of cases. *Staphylococcus aureus* infections never primarily involved the central nervous system. They were always related to infections outside the central nervous

system, like endocarditis or pneumonia, which then spread to cause meningitis. *Haemophilus influenzae* was the next most common pathogen accounting from between 4 – 5 percent of the cases. Streptococci including Group A streptococci, Group B streptococci, enterococci, Group D non-enterococci, and viridans streptococci also caused cases of meningitis in both decades. Group B streptococci caused 1 percent of cases in the 1980s but in the 1990s, 7.6 percent of cases were caused by that organism. Gram negative bacteria caused between 4 – 5 percent of cases. Meningitis caused by *E. coli* usually had its origin in infections that involved the urinary tract. In the 1990s, one case of *E. coli* meningitis occurred in a man from a developing country that was on steroids and had disseminated strongyloidiasis as an underlying condition. The *Enterobacter* isolate came from a patient with meningitis, sepsis, and lupus. The *Pseudomonas aeruginosa* meningitis was in a man who was status post-coronary artery bypass graft. He had a saphenous vein infection with *Pseudomonas aeruginosa*, subsequent bacteremia and then developed meningitis. The etiology of bacterial meningitis on the Parkland Memorial Hospital medical service in the 1990s as opposed the 1980s is roughly equivalent, except for the emergence of Group B streptococci as an important pathogen. The difference in occurrence (1/100 vs. 7/92) is statistically significant, p=0.02, Fisher's exact test. In both decades, approximately 15 percent of cases of bacterial meningitis do not have a positive culture or a positive antigen test and have not been included in the table.

In pneumococcal meningitis, prognostic factors include age, underlying disease, state of consciousness on admission into the hospital, pneumonia, and complications during the stay. As analysis of case series of pneumococcal meningitis undertaken during the 1980s detailed that the case fatality rate varied by the incidence of pneumonia in the patients. Provided that one corrected for the incidence of pneumonia, steroid therapy did not influence the case fatality rate in pneumococcal meningitis. *Streptococcus pneumoniae* has become increasingly non-susceptible to penicillin. Penicillin susceptible strains have an MIC of 0.06 micrograms per milliliter or less. Penicillin intermediate strains have an MIC of 0.1 – 1.0 micrograms per ml and at Parkland Memorial Hospital constitute 27 percent of 54 isolates collected during the last half of 1998. High level resistance to penicillin includes isolates with a MIC of 2 micrograms per ml or greater and accounted for 7 percent of Parkland isolates during the same interval. Seven percent of the 54 isolates studied at Parkland were resistant to concentrations of cefotaxime and ceftriaxone that could be achieved in the CSF. Since penicillin does not penetrate the blood brain barrier well, 34 percent of pneumococcal isolates could not have been treated successfully with penicillin. Seven percent of pneumococcal isolates could not have been treated with cefotaxime or ceftriaxone. In all probability, intermediately susceptible isolates to penicillin could be treated with penicillin alone provided they were localized to a site other than the central nervous system, the eye, or the middle ear. If pneumococci cannot be treated with penicillin, cefotaxime or ceftriaxone, they should respond to vancomycin therapy. In adults in a Spanish study, vancomycin at 30 mg per Kg per day coupled with the simultaneous

Pneumococcal Meningitis

- Prognostic factors: age, underlying disease, state of consciousness on admission, pneumonia, complications during stay.
- Antibiotic therapy. PCN susceptible 0.06 mcg/ml or less. PCN intermediate 0.1-1.0 mcg/ml (PMH 27%). PCN high level resistance 2 mcg/ml (PMH 7%).
- Vancomycin at 30 mg/kg led to clinical failure in 4/ll cases of pneumococcal meningitis. The 4 cases completed therapy with ceftriaxone.

administration of dexamethasone led to clinical failure in four of eleven cases of pneumococcal meningitis that were treated. These four cases either had an increase in fever or clinical failure shown by a worsening mental state. The four cases that originally failed with vancomycin completed therapy successfully with ceftriaxone. Since there are reported vancomycin failures, the initiation of antibiotic therapy in pneumococcal meningitis with a positive gram stain and before cultures and susceptibilities can be completed, involves the use of vancomycin at 50 mg per Kg per day and coupling it with either cefotaxime or ceftriaxone. This is a high dose of vancomycin and necessary adjustments need to be made for renal dysfunction and obesity or ototoxicity may develop. Once susceptibility studies are completed and the isolate has been determined to be susceptible to penicillin, that drug should be given to complete a 14-day course.

The use of steroids in bacterial meningitis has been widely debated. In case series of patients with pneumococcal meningitis before 1988, the case fatality rate varied directly with the incidence of pneumonia in the population and there was no effect seen with steroid therapy. In placebo controlled trials at Children's Medical Center in Dallas, Texas, Dr. McCracken and his associates found that the addition of dexamethasone either with or before the initiation of ceftriaxone in *H. influenzae* meningitis lowered the incidence of severe hearing loss from 15 – 3 percent. There was no effect on case fatality rate. Although some investigators have not found an effect, perusal of the complete data by experts leads most to the conclusion that dexamethasone therapy should be initiated for *H. influenzae* meningitis in infants and children before or concomitantly with ceftriaxone. A retrospective Spanish study of cases of pneumococcal meningitis found beneficial effects of steroids on the case fatality rate. A retrospective study of 97 pediatric cases of pneumococcal meningitis at Children's Medical Center deduced that steroids were effective. In a study combining children and adults published in 1989 and conducted at an Egyptian fever hospital, 429 patients with bacterial meningitis were admitted. Antibiotic therapy consisted of ampicillin and chloramphenicol. Dexamethasone was given to one group and a placebo to the other. The dexamethasone treatment group and the placebo were comparable with regard to age, sex, duration of symptoms, and state of consciousness at the time of hospitalization. There was no difference in case fatality rates between the two treatment groups with regard to meningococcal meningitis or meningitis due to *H. influenzae*. There was, however, a statistically significant reduction in the case fatality rate in pneumococcal meningitis in patients that received dexamethasone. Only seven of 52 patients died in the steroid treated group with 22/54 patients dying that did not receive dexamethasone. A statistically significant difference in deafness was observed between the dexamethasone and placebo treated patients. None of the 45-surviving patients receiving steroids had hearing loss where 4/32 patients not receiving dexamethasone had severe hearing loss. The study grouped all patients >25 years of age into one category and did not further analyze patients by whether or not they had pneumonia. In the Fever Hospital study, the patients were given dexamethasone at an adult dosage level of 24 mg/day. Most pediatric studies that have utilized dexamethasone in treatment of bacterial meningitis emphasize that their utility is

Pneumococcal Meningitis

- Initiating antibiotic therapy: vancomycin at 50 mg/kg + cefotaxime or ceftriaxone.
- Steroid therapy. Trials before 1988. Abbassia Fever Hospital trial: case fatality rate = 7/52 steroid vs. 22/54 non-steroid. Retrospective Spanish study. Retrospective study of 97 pediatric cases.
- Steroids most effective if begun before or within 8 hours of antibiotic administration and continued only for 2 days (pediatric studies).

optimized when the steroid is initiated within 8 hours of antibiotic administration and that the best time period for its administration should be two days or less.

Definitive studies supporting the routine use of steroids in adult bacterial meningitis remain to be performed. The Egyptian Fever Hospital study suggests that their use in pneumococcal meningitis may lower the case fatality rate. Other studies have not supported this contention despite the fact that the subject has been under study for over 40 years. Some authorities advise their use when signs of intracranial hypertension are present. There is no evidence in adult patients that the course of disease with other pathogens is consistently altered. Steroid therapy generally lowers antibiotic entry into the CSF because inflammation is lessened. Pediatric studies suggest that if steroids are used, they should be given early in illness and only for a short time.

Meningitis due to *Listeria monocytogenes* is becoming better understood. It has a predilection for immunosuppressed patients such as transplant recipients and persons with lymphoma. However, it can occur in elderly patients and alcoholic persons. It can also occur in immunologically normal adults in the peripartum period. Its variation in incidence probably can be linked best to the fact that the major mode of transmission of *Listeria monocytogenes* is most probably food borne. In surveys of normal persons, it has been found that 2 – 4 percent of study participants may transiently excrete the organism in stool. In a study performed with sporadic cases of *Listeria* meningitis, the organism was cultured from food in as many as 75 percent of the home refrigerators of the cases. Although *Listeria* meningitis usually presents as purulent meningitis with thousands of cells, a low glucose and a high protein concentration, it can also present as granulomatous meningitis, with tens to hundreds of cells, a lowered glucose and a high protein concentration. A classic but rare complication of *Listeria* meningitis is its capacity to produce abscesses in brain localized around the fourth ventricle. *Listeria* rhombencephalitis results and has an overall mortality of 51 percent. Its manifest signs are explained by involvement of the brainstem and cerebellum around the fourth ventricle. Cranial nerve palsies are seen as well as cerebellar signs and hemiparesis. There can be mental impairment and unconsciousness. The structures involved control vital functions such as respiration, swallowing, and phonation. Since *Listeria* rhombencephalitis involves abscess formation in the brain, antibiotic therapy may have to be prolonged for four to six weeks or more. In immunologically normal patients, therapy for *Listeria* monocytogenes meningitis can be finished in two weeks, usually with a drug like ampicillin, penicillin, sulfatrimethoprim, or vancomycin. In immunosuppressed patients, therapy may have to be prolonged to four weeks. There are isolated reports of vancomycin failure at 30 mg per Kg per day but no reports of failure at 50 mg per Kg per day.

Listeria Meningitis

- Major mode of transmission is probably food-borne.
- 2-4% of persons may transiently excrete the organism in stool.
- In sporadic cases, the organism has been cultured from 75% of home refrigerators.
- Listeria rhombencephalitis: cranial nerve palsies, cerebellar signs, hemiparesis and impairment of consciousness. Overall mortality 51%.
- Isolated reports of vancomycin failure at 30 mg/kg.

Group B streptococci have increased their incidence form 1 percent during the 1980s to 7.6 percent of cases in the 1990s. In total, eight patients have incurred Group B streptococcal meningitis and have been hospitalized at PMH from 1985 to the present. The largest reported series of Group B streptococcal meningitis in a single hospital occurred in a Spanish hospital series that included 12 cases. Another study reported four cases. The eight cases at Parkland consisted of one patient who had meningitis in association with middle ear disease. The other seven patients consisted of two patients with insulin dependent diabetes mellitus, two patients with cirrhosis, one patient with lupus and three immunologically normal persons. Three of the eight or 37.5 percent died from their meningitis. The patient with diabetes, one of the patients with cirrhosis, and one immunologically normal adult died from their disease. In the 1990s, Group B streptococci have emerged as the third most common pathogen causing bacterial meningitis on the medical service at PMH. These organisms are usually highly penicillin susceptible and almost always can be treated with penicillin alone. Although since they cannot be distinguished from *S. pneumoniae* except by culture, initial therapy should consist of cefotaxime or ceftriaxone plus vancomycin.

Group B Streptococcal Meningitis in Adults

- Largest reported series from Spain included 12 adults. Another series reported 4 adults.
- Since 1985, 8 adults were seen at PMH. 7/8 were bacteremic. 3 died.
- One patient had CSF otorrhea, 2 had DM, 1 had lupus, 2 had cirrhosis, 2 were normal (24 and 29 years old).
- The patients with DM and lupus and the 29-year-old man died.

Gram negative bacteria other than *H. influenzae* have caused five cases of meningitis in the 1980s and four in the 1990s. In all but one of these cases, the cause of the meningitis was an infection outside the central nervous system. The *E. coli* cases usually had a urinary tract infection except for the patient with disseminated strongyloidiasis. The *Enterobacter* case was in a patient with lupus and sepsis. The patient with *Pseudomonas aeruginosa* meningitis was status post-coronary artery bypass graft. The saphenous vein harvest site became infected with *Pseudomonas aeruginosa*; bacteremia and meningitis ensued. The patient with *K. pneumoniae* was an 82 year-old man with no clinically apparent source for the organism. Of these nine patients, all died as a result of their infection. All of the patients were elderly with the exception of the patient with meningitis due to *Ps. aeruginosa.*

Gram Negative Bacillary Meningitis*

- *E. coli:* 6 cases; 5 with UTIs; 1 patient had disseminated strongyloidiasis
- *K. pneumoniae:* 1 case in a man 82 years old
- *E. cloacae:* 1 case in a patient with lupus and sepsis
- *Ps. aeruginosa:* 1 case in a man with a saphenous vein harvest site infection

*Excluding *H. influenzae*

Twenty-four patients having trauma, cranial or spinal surgery were studied for their etiologies during the 1980s. This series was compared to 32 comparable patients having trauma, neurosurgery, or other cranial surgery during the 1990s. A variety of organisms most of them hospital-acquired appeared as the etiological agents in neurosurgical meningitis. There appears to be no statistically significantly different trend in the types of organisms isolated from the patients.

Most of the organisms can be treated with vancomycin plus the addition of ceftazidime. The usual regimen for treating such a patient is to initiate vancomycin at an adult dosage equivalent to 50 mg per Kg per day and ceftazidime 2 gm q 8 hours. Treatment is usually for 14 days after the last positive CSF culture. Since ceftazidime has been losing its efficacy against Enterobacter and Citrobacter species, cefepime and meropenem have begun to be more commonly utilized. However, cefepime and meropenem are under investigation for meningitis and have not been approved by the FDA for this indication. For gram negative bacteria under the usual circumstance, a single antibiotic is generally effective. Aminoglycoside therapy is usually not necessary except in the initial phases when the medication can be given into the ventriculostomy. Of concern is the single report of Acinetobacter species that caused meningitis; during therapy with meropenem the isolate acquired resistance and the patient subsequently died from his infection.

Table 2
Etiology of Purulent Meningitis Following Trauma or Surgery

	1980s*	**1990s****
S. aureus		
Methicillin sensitive	4 (16)	
Methicillin resistant	1 (4)	1 (2.9)
Unspecified		12 (36.4)
Coagulase negative staphylococcus	4 (16)	4 (11.8)
Group B streptococcus		1 (2.9)
Enterococcus	1 (4)	2 (5.8)
Viridans streptococcus	1 (4)	2 (5.8)
S. pneumoniae		*1 (2.9)*
N. meningitidis		*1 (2.9)*
Gram negative bacteria		
P. aeruginosa	4 (16)	
S.. marcescens	3 (12)	
K. pneumoniae	3 (12)	
E. aerogenes		1 (2.9)
E. cloacae	2 (8)	3 (8.7)
Acinetobacter sp.		1 (2.9)
E. coli	1 (4)	1 (2.9)
H.. influenzae	1 (4)	2 (5.8)
Candida albicans		2 (5.8)

*25 etiologic agents in 24 patients. No. (%)
**34 etiologic agents in 32 patients. No. (%)

Thus, empiric antibody therapy in bacterial meningitis in adult medicine consists of vancomycin plus cefotaxime or ceftriaxone. If *Listeria* is documented by gram stain, ampicillin can be substituted for the vancomycin or one could use all three antibiotics. For neurosurgery, vancomycin plus ceftazidime is a reasonable empiric combination of antibiotics. Cefepime and meropenem are under investigation, have not been FDA approved for this indication but are being increasingly used in practice due to emerging resistance to ceftazidime.

Empiric Antibiotic Therapy in Bacterial Meningitis

- Medicine: vancomycin + cefotaxime or ceftriaxone +/- ampicillin
- Neurosurgery: vancomycin + ceftazidime. Cefepime and meropenem under investigation.

Granulomatous Meningitis

In granulomatous meningitis, the cell count is in the tens to hundreds, the glucose is lowered usually below 25 mg per dL and the protein concentration is elevated often to high levels. The most common cause of granulomatous meningitis at Parkland Memorial Hospital is cryptococcal meningitis. The second most common cause is tuberculous meningitis. The diagnosis of tuberculous meningitis has been aided by the development of a polymerase chain reaction for the detection of *Mycobacterium tuberculosis* in body fluids and sputum. The third most common cause of granulomatous meningitis is carcinoma or lymphoma. Fungi are a fourth cause, either usually being histoplasmosis or coccidioidomycosis. With regard to histoplasmosis, the emergence of the histoplasma antigen test, has been an advance. Histoplasma antigen can be detected in urine or CSF usually by a radioimmunoassay or an ELISA based assay. Other frequent causes of granulomatous meningitis include neurocysticercosis and sarcoidosis. In toxoplasmosis, the sugar may be normal or depressed. In syphilis, the CSF glucose is usually normal but may be depressed. Although *Listeriosis* presents more usually as a purulent meningitis, it can present as a granulomatous meningitis. Other causes include Brucellosis, Nocardiosis, Whipple's disease, and other fungi most specifically sporotrichosis and candidiasis. It should be noted that mucormycosis and aspergillosis as well as blastomycosis infrequently cause meningitis. Aspergillosis and mucormycosis more commonly cause brain masses or brain abscesses in people who have infection with these agents. Viruses can cause a lowering of the CSF glucose. In mumps and lymphocytic choriomeningitis (LCM), a modest lowering of the CSF glucose is common. A lowering of the CSF glucose can be seen occasionally but rarely in patients with central nervous system infection with the herpes viruses, namely herpes simplex virus (HSV), varicella zoster virus (CZV), and cytomegalovirus (CMV). In cytomegalovirus infections in AIDS, the *cauda equina* syndrome can occur. Patients have involvement of the *cauda equina*, a CSF polymorphonuclear leukocytosis and a low glucose. CMV can usually be identified by PCR in the CSF of these cases.

Granulomatous Meningitis
The Most Frequent Etiologies

- Cryptococcal meningitis
- Tuberculous meningitis
- Carcinoma, lymphoma
- Fungi (histoplasmosis, coccidioidomycosis)
- Cysticercosis
- Sarcoidosis
- Toxoplasmosis

Granulomatous Meningitis
Less Frequent Etiologies

- Syphilis
- Listeriosis
- Brucellosis
- Nocardiosis
- Whipple's disease
- Other fungi (sporotrichosis, candidiasis)
- Viruses (mumps, LCM, HSV, VZV, CMV)

Benign causes of granulomatous meningitis exist but are rare. There is an entity known as granulomatous or chronic meningitis of unknown etiology. These people can have disease courses of months to years, have benign outcomes and spontaneously recede without any specific therapy. There are individual reports and series of these patients but they must be infrequent. Other benign causes exist but are more easily recognized. As a subarachnoid hemorrhage evolves, there can be a polymorphonuclear leukocytosis in response to the irritant effect of the hemorrhage that is then followed by a lymphocytosis. The development of hypoglycorrhachia occurs as the products of this evolving subarachnoid hemorrhage saturate the glucose transport system and limit penetration of glucose into the cerebrospinal fluid. Chemical meningitis now is infrequent but colloidal substances like radioiodinated serum albumin were once given directly intrathecally and could cause a CSF formula indistinguishable from that of granulomatous meningitis.

Granulomatous Meningitis

- Chronic meningitis of unknown etiology, evolution of a SAH and chemical meningitis should be added to the differential diagnosis
- Benign causes of granulomatous meningitis are infrequent
- Making a diagnosis of granulomatous meningitis infers a commitment to securing a specific diagnosis and initiating therapy

Overall, it is apparent that benign self-limited causes of granulomatous meningitis are infrequent in comparison to instances where there are defined and where the course, unless modified by specific therapy, may significantly affect the patient and cause death. Making a diagnosis of granulomatous meningitis infers a commitment to securing a specific diagnosis and initiating therapy. Appropriate consultation may be necessary as well as empiric therapy. An illustrative example is to consider *Mycobacterium tuberculosis* and its potentially devastating effect on the central nervous system, the relative difficulty in making a specific diagnosis, and the seriousness with which this problem must be managed.

The pathology of tuberculosis meningitis consists of a granulomatous, inflammatory process that predominates at the base of the brain. The basilar meningitis entraps and infiltrates the nerves, which travel through it. Cranial neuritis is a known complication of tuberculous meningeal disease. There can be parenchymal granuloma formation within the brain, which can lead to scarring. Hydrocephalus can be obstructive. Absorptive hydrocephalus occurs when production of CSF exceeds absorption and there is an excessive accumulation of CSF. This leads to intracranial hypertension in which the CSF at increased pressure is symmetrically distributed within the thecal sac. Tuberculous meningitis is mainly obstructive; in cryptococcal meningitis it is generally absorptive. There may be the formation of tuberculomas or tuberculosis abscesses. Tuberculomas usually consist of small amounts of antigen in association with relatively few mononuclear cells and a profound cellular immune response. Tuberculomas can grow under therapy and can coalesce forming larger

The Pathology of Tuberculous Meningitis

- Basilar meningitis
- Cranial neuritis
- Parenchymal granuloma formation
- Hydrocephalus (obstructive, absorptive)
- Tuberculomas, tuberculous abscesses
- Gyritis, cerebral edema
- Granulomatous arteritis (basal ganglia, thalamus, pons, spinal cord infarcts)
- Thrombophlebitis, dural sinus involvement
- Arachnoiditis

structures, which may have to be surgically drained or excised. Tuberculosis abscesses consist of abscesses within the brain with many polymorphonuclear leukocytes and an abundance of organisms. In the treatment of tuberculomas, corticosteroid therapy may be needed. Patients can develop cerebral edema and gyritis. Gyritis is an intense inflammation located to the superficial gray matter, caused by invasion of the organism and the cellular immune response. Since the Circle of Willis and its branches lie at the base of the brain, granulomas can involve arteries and a granulomatous arteritis may ensue with infarct formation. Infarcts are particularly likely to involve the basal ganglia, the thalamus, the pons, and the spinal cord. Of less importance than in purulent meningitis, thrombophlebitis and dural sinus involvement may develop. Arachnoiditis is constant and actual arachnoid masses may form with an ensuing spinal subarachnoid block. Again, the use of steroid therapy is hotly debated. Its been found not to help in mild or advanced cases, but there is moderate evidence that it may be beneficial in moderately severe cases with intracranial hypertension, in the therapy of tuberculomas or in patients who are having infarcts as a result of granulomatous arteritis.

Encephalitis

Patients with aseptic meningitis have a fever, a stiff neck and a headache. In addition to these manifestations, patients with encephalitis also have a disturbance in brain function. On LP, both groups of patients have CSF lymphocytosis, a normal glucose and an elevated protein concentration. Encephalitis can be divided into primary infectious and post-infectious categories. A classical case of primary infectious encephalitis is exemplified in herpes simplex encephalitis (HSE) where the virus is present in brain and its DNA in the CSF. In HSE, the virus is directly cytocidal and a specific immune response occurs directed against the virus. The CSF virus antibody index increases, i.e., the amount of antibody that is being formed directly within the CSF. There are also virus specific T-cell responses in the brain and CSF. The pathology consists of perivascular infiltrates and microglial

Primary Infectious		**Post-Infectious Encephalitis**
• Primary, e.g., HSE • Virus is present in brain, CSF • An immune response occurs directed against the virus – Virus Ab Index increases – Virus specific T cell responses • Perivascular inflammation, microglial nodules (gray matter)	**Vs**	• Post-infectious, e.g., rubeola • Virus is absent from brain, CSF • Immune dysregulation ensues – T cells attack antigens like the basic protein of myelin • Perivenous demyelination (white matter)

nodules occurring primarily in gray matter. As opposed to primary infectious encephalitis, post-infectious encephalitis is classically exemplified by rubeola where as so far as is known, the virus is absent from brain and the CSF. The infection initiates a state of immune disregulation in which T lymphocytes attack antigens like the basic protein of myelin causing perivenous demyelination seen usually within white matter.

Herpes simplex encephalitis is the most common sporadic encephalitis in the world. Its rate approximates 1 in 250,000 to 1 in 500,000 persons per year. Herpes simplex encephalitis can occur in neonatal herpes, in primary infections after the neonatal period and as reactivation infection. Most cases of HSE result from reactivation infection. In first episode, true primary cases of genital herpes, HSV can make its way into the meninges where it causes aseptic meningitis. This illness can be quite dramatic with up to a thousand cells in the CSF concomitant with the genital eruption. In the usual case of HSE, the patient is older and the virus is thought to reactivate from a latent state in the trigeminal ganglion. With reactivation, the virus travels via axonal flow to the meninges underlying the temporal lobe. The virus invades the temporal lobe destroying neural tissue as the disease process progresses. A necrotising, hemorrhagic encephalitis ensues directly related to the presence of the virus in brain. Temporal lobe localization is a hallmark of reactivation disease. The contralateral temporal lobe can be involved independently and progress by spread into the adjacent frontal and the parietal lobes. The diagnosis is made by consideration of the temporal lobe localization (olfactory hallucinations, seizures) and the involvement of the motor strip. Disturbances in speech are common and a progressive hemiparesis can occur with the mouth and hand being involved first. The LP shows CSF pleocytosis, sometimes xanthochromia, a normal glucose and a high protein concentration. The critical issue in managing such patients is making an exact rapid diagnosis. Such diagnosis required brain biopsy of the involved temporal lobe; however, there have been major improvements in technology to diagnose HSE. A polymerase chain reaction (PCR) on the CSF is now able to be performed and tests for HSV DNA. This is a very sensitive and specific test. The presence of a positive PCR for HSV DNA in the CSF makes a definitive diagnosis if a competent laboratory does the testing. A PCR on the first sample of CSF is usually positive; if negative it may be positive with the second LP performed a couple of days later. Concomitant with the presence of HSV DNA, there is a rise in the HSV antibody index denoting a specific intrathecal synthesis of antibody. To calculate the HSV antibody index necessitates dividing the HSV antibody titer in CSF by the CSF albumin concentration and this quotient is divided by the plasma HSV titer divided by the plasma albumin concentration. Characteristic MRI findings occur within a few days of illness onset and show temporal lobe involvement. Once the diagnosis is suspected, acyclovir 10 mg/Kg q 8 hrs can be initiated intravenously and continued for at least 14 days. If the PCR is persistently negative and there is evidence of a temporal lobe lesion, this constitutes evidence that another disease process is occurring and a

Encephalitis PMH & ZLUH (6/94-5/99)

- 29 adult cases; 26 at PMH, 3 at ZLUH
- 0 HSE, 11 St.LE, 2 VZV, 1 CMV, 15 Unk. Etiology
- 3 Jan.-Mar.; 10 Apr.-June.; 14 July-Sept.; 2 Oct.-Dec.
- 17 males and 12 females
- 4 deaths within 30 days after onset

Herpes Simplex Encephalitis

- Most common sporadic encephalitis. Rate approximates 1/250,000 per year
- Occurs in neonates, in primary and in reactivation infection
- Reactivation infection most common
- Temporal lobe localization is usual
- Diagnosis: PCR, rise in HSV Ab Index, brain biopsy. Characteristic MRI.
- Therapy: ACV for at least 14 days

brain biopsy may be necessary to resolve the issue. The use of acyclovir has decreased the case fatality rate from 70 – 30 percent and although many of the patients improve, a significant amount of residual abnormalities may persist due to the highly necrotic nature of the disease process. Herpes simplex encephalitis can occur in primary disease after the neonatal period. Here the virus may go to the brain by a hematogenous route, although the temporal lobe also tends to be predominately involved. However, multiple sections of the brain can also be involved. The characteristic MRI pattern in primary infection is that of an expanding lesion(s) which is directly related to the cytocidal effect of the virus in the brain at the point where invasion and viral replication has occurred.

After the occurrence of HSE, there are reports of recurrent encephalitis. The pathogenesis of these recurrent episodes remains to be elucidated but when an LP is done, the CSF PCR for HSV tends to be negative and the HSV antibody index remains stable. This has been interpreted as indicating that the recurrent encephalitis is immunologically mediated. However, in selected cases a culture of brain biopsy has been done by cocultivation techniques and in some instances, this culture has been positive pointing to the fact that the virus is still present in brain. Therapy of recurrent disease is with intravenous acyclovir +/- the addition of steroids. Although there are reports of brain stem encephalitis, transfer myelitis and other disease entities due to HSV, these tend to be in the minority of cases. In the majority of instances, temporal lobe involvement is the most highly characteristic feature of HSE.

Post-HSE Encephalitis

- After HSE, there are reports of recurrent encephalitis
- In these cases, the CSF PCR for HSV is negative and the HSV Ab Index remains stable
- However, brain biopsy cultures in such cases by cocultivation techniques may be positive
- Therapy consists of ACV +/- steroids

St. Louis encephalitis is an arbovirus that periodically spills over to involve cities in the form of summer – fall urban outbreaks. Dallas, Texas has had major outbreaks in 1966, 1975, and 1995. Houston, Texas has had multiple recurrent outbreaks and its last epidemic occurred in 1991 and involved 41 patients. Four of 19 patients who were tested in Houston were infected with HIV. St. Louis encephalitis virus affects elderly adults most commonly. There are approximately 250 infections for each clinical case. In 1995, an area around Fair Park flooded during May. The storm sewer draining surface water from the area remained filled with water during the summer and mosquito pools breeding in that storm sewer became infected with St. Louis encephalitis virus. In August and September, 21 cases occurred in Dallas County, eleven of which were hospitalized at PMH. In the 1995 epidemic, residence in an area flooded that spring, age and homelessness affected attack rates. Homelessness and alcoholism as a surrogate marker characterized persons who tended to remain out of doors during early evening and were unprotected from mosquito exposure. Since St. Louis encephalitis and Western equine

St. Louis Encephalitis

- Periodic Texas urban epidemics (Dallas, TX 1966, 1975, 1995)
- Occurs most commonly in elderly adults
- In 1995, residence in an area flooded that spring, age, and homelessness affected attack rates
- Overall case-fatality rate 10%; in aged 20%
- Diagnosis: IgM IFA tests on first serum almost always +
- Radiology: Unique radiological sign: Hyperintense substantia nigra on T2 weighted imaging

encephalitis viruses were isolated from rural Dallas County that summer, the Fair Park epidemic may have resulted from spillover of this rural cycle into the city. The overall case fatality rate in St. Louis encephalitis is 10 percent but in aged persons it may reach 30 percent. If the patient survives, they have long convalescent periods but they are thought usually to recover completely. The diagnosis can now be made rapidly by submission of the first serum specimen obtained from the patients to an appropriate laboratory. An indirect fluorescent assay for IgM antibody is performed and is usually positive. Thus, the exact viral diagnosis can be given to the caring physician within the same day as the test specimen is submitted. The patient has to be reported to public health authorities and rapid viral diagnosis acts to concentrate mosquito control activities into the areas of the city that are actually involved by the infected vectors.

In the 1995 epidemic at PMH, CT scans and MRIs were performed on all the patients. MRIs were performed on seven of the eleven cases. In two of these cases, there was a unique radiological sign, not having been previously described in the literature. There was a bilateral hyperintense signal in the substantia nigra on T2 weighted imaging. In one of the cases, the hyperintensity appeared asymmetric. Both of the patients from whom these abnormal MRIs were taken were young persons who were severely ill. One patient had diffuse tremulousness and the other marked rigidity. Pathologic examinations of the substantia nigra have been made and they showed that this structure is the most heavily involved portion of the human brain in terms of the volume of inflammatory lesions. This radiological finding correlates with the clinical observations that tremulousness and rigidity are a major part of the neurological abnormalities in St. Louis encephalitis.

Once a diagnosis has been made, the patient should be watched carefully and treated appropriately for the syndrome of inappropriate antidiuretic hormone secretion. Antibiotics can often be discontinued. In the 1995 Dallas epidemic, two out of 21 patients were HIV antibody positive. Thus, in two Texas epidemics, six of 40 patients tested were HIV infected. It is not known whether HIV infection predisposes the patient to disease once infected with St. Louis encephalitis virus or whether this represents a sampling phenomenon because both of these epidemics occurred in areas where there may have been a higher prevalence of HIV infection.

There were 29 cases of encephalitis in the five-year period ending in May 1999 at PMH and ZLUH. Eleven of these were due to St. Louis encephalitis, two due to varicella zoster virus, one due to cytomegalovirus, and 15 were of unknown etiology. There were no cases of herpes simplex encephalitis but this is unusual since we usually have one or two a year at the medical center. The remainder 15 cases were patients who had encephalitis of unknown etiology. Two of these 15 (13%) died. There were eight males and seven females. Three had onsets in January and March, seven during April and June, three during July and September, and two during October and December. Encephalitis of unknown etiology is a common problem in Dallas and in other parts of the world and has, for the most part, resisted the efforts of investigators

Encephalitis of Unknown Etiology

- 5 years PMH, ZLUH: 15 cases, 2 deaths (13%), 8 males, 7 females. 3 Jan.-Mar., 7 Apr.-June, 3 July-Sept., 2 Oct.-Dec.
- Usually, cases predominate in young-middle aged men in summer and early autumn, vary by year and the case-fatality rate = 10-15%.
- Most cases concentrated geographically, e.g., SE, SW U.S.
- Candidate agents include enteroviruses (E71), arboviruses, HHV-6.

to find candidate etiologic agents. Usually, the epidemiology shows that cases predominate in young to middle aged men in summer and early autumn, vary by year and case fatality rate is 10 – 15 percent. The series accumulated at PMH and ZLUH tends to be unusual in that in the last five years there has not been the usual summer and early autumn occurrence of cases. Most cases of encephalitis of unknown etiology are concentrated geographically. Two areas of which the country in which this concentration is most evident are the southeastern and southwestern United States. Although efforts have been made to isolate viruses from these patients, there are no likely candidate viruses that could account for all the cases. Current candidate agents include enteroviruses, arborviruses and HHV-6. Enterovirus 71 can cause hand, foot and mouth disease, flaccid paralysis and encephalitis. This virus is found sporadically in the United States. It has just recently been epidemic in Taiwan where there were approximately 160,000 cases and where deaths involved mostly younger aged children. Arborviruses could be involved and in certain areas in the country there have been new agents discovered. In New York State, Jamestown Canyon virus is now known to be an important cause of encephalitis in that area of the country. Human herpes virus 6 (HHV-6) has been implicated as an agent of focal encephalitis. The National Institutes of Allergy and Infectious Diseases Cooperative Antiviral Study Group accumulated CSF specimens from patients with presumed HSE and found that a number that were negative for HSV had a positive PCR for HHV-6. A prospective study needs to be performed to evaluate HHV-6 in human encephalitis.

Aseptic meningitis is generally seen in young children and in adults that have contact with them. It is generally mostly an illness of discomfort and has virtually no mortality. It has to be distinguished from bacterial meningitis so lumbar punctures are usually performed. PCR has been utilized to detect enteroviruses in the CSF. The PCR detects a nucleotide sequence near the 5 ' coding region, which most enteroviruses have in common. Recently an interesting compound has become available which has been tested in pediatric and adult populations for its efficacy against enteroviruses. The drug name is pleconaril and it is a low molecular weight compound that prevents viral attachment and uncoating by integrating into a hydrophobic pocket of one of the major coat proteins of the enterovirus, viz., VP-1. The compound is readily bio-available and when given at 400 orally three times a day for 7 days, a mean peak serum concentration of 3 μgm/mL results. This is far above the MICs found for most enteroviruses. In the rat, pleconaril was concentrated in the brain, spinal cord, and meninges to a concentration higher than seen in the serum of the patients. This drug has been given to children with immunodeficiency states who have chronic meningitis with an enterovirus and has shortened the time to clearance of the virus in a manner superior to intravenous immunoglobulin. In an exploratory trial in the treatment of aseptic meningitis in adults, patients given a placebo compound had a mean of 9.5 days of illness compared to 4 days in the group given pleconaril. The study has been repeated in a larger group of children with comparable results. The further development of the drug can be watched with interest.

Pleconaril and Enterovirus Aseptic Meningitis

- Pleconaril is a low molecular weight compound that prevents viral attachment and uncoating by integrating into a hydrophobic pocket of VP1.
- 400 mg po TID for 7 days resulted in a mean peak serum concentration of 3 mcg/ml. In the rat, pleconaril is concentrated in the brain, spinal cord and meninges.
- In an exploratory trial in adults, the placebo group had a mean of 9.5 days of illness compared to 4 days with pleconaril.

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