CNS Infections: Progress and Problems

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CNS INFECTIONS: PROGRESS AND PROBLEMS

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The etiologies of community acquired bacterial meningitis in adults are multiple. In Table 1, three series of cases are summarized. The first series from Parkland Memorial Hospital was collected from 1980 through 1999 and consisted of 226 cases.

Table 1: Etiologies of Community-Acquired Bacterial Meningitis in Adults

	PMH 1980-1999	MGH 1962-1988	EDABMS 1993-2001
Cases	**226**	**253**	**301**
% of Cases			
S. pneumoniae	47	38	36
N. meningitidis	13	14	32
L. monocytogenes	5	11	2
S. aureus	5	5	1
Streptococci	7	7	4
H. influenzae	4	4	1
Gram negative bacilli	4	4	1
Other	0	2	1
Culture negative	15	13	22

The second series, is from the Massachusetts General Hospital, was collected between 1962 and 1988 and consisted of 253 cases. In the Massachusetts General Hospital series, the total number of cases of meningitis reported was 493 but 140 of these were hospital-acquired cases. The third series examined is the European Dexamethasone Against Bacterial Meningitis Study (EDABMS) and consisted of 301 patients enrolled between 1993 and 2001. In all three series, *Streptococcus pneumoniae* was the leading pathogen accounting from 36% to 47% of cases. The case fatality rate of

Streptococcus pneumoniae meningitis at PMH was 35%, at MGH it was 28% and in the EDABMS in placebo recipients it was 34%. *Neisseria meningitidis* was the second most common pathogen in all series accounting from 13% to 32% of cases. The case fatality rate of meningitis from this organism was 15% at MGH and 3% in the EDABMS. *Listeria monocytogenes* was the third most common pathogen accounting for between 2% and 11% of cases. *S. aureus* accounted for between 1% and 5% of cases while streptococci caused between 4% and 7% of cases. The PMH experience with streptococci is of interest because in the 1980's there was only one case of Group B streptococcal meningitis where in the 1990's there were 7 cases of Group B streptococcal meningitis. At PMH in the total 20-year period, *Listeria monocytogenes* accounted for 11 cases whereas Group B streptococci accounted for 8 cases. In the combined series, *Haemophilus influenzae* accounted between 1% and 4 % of cases while gram-negative bacilli like *E. coli*, *E. cloacae*, *K. pneumoniae*, and *Ps. Aeruginosa* accounted for between 1% and 4% of cases. Culture negative cases accounted for 13% to 22% of cases. Culture negative cases represent a group that may be heterogeneous because not all of the cases so designated may actually have been caused by bacteria. For instance, in this group there may be cases of drug-induced aseptic meningitis (DIAM) or even viral meningitis that initially presented with a high number of white blood cells in the cerebrospinal fluid (CSF) that were composed predominantly of polymorphonuclear leukocytes. The cases at PMH were the results of a survey over a 20-year period and averaged approximately 1 case per month.

At PMH there has been an increasing resistance of *S. pneumoniae* to penicillin (Table 2). In 1993, only 2% of isolates had either intermediate or high- level

Table 2: Resistance of *Streptococcus Pneumoniae* to Penicillin (PMH)

	No. Isolates	Intermediate Resistance	High-Level Resistance	Total
1993	125			2%
1993	129			9%
1996	66			12%
1997	102			27%
1997	61			34%
1999*	60	28%	8%	36%
2000*	99	24%	23%	47%
2002	149	12%	17%	29%
2003	82	28%	12%	40%

* 8-17% *S. pneumoniae* isolates had intermediate or high level resistance to cefotaxime and/or ceftriaxone.

Data compiled by Drs. Paul Southern and Rita Gander

resistance to penicillin. Resistance to penicillin rose to 47% in the year 2000 and in 2003, presently is 40%. Intermediate resistance to penicillin accounted for between 12% and 28% of isolates; high-level resistance to penicillin accounted for between 8% and 23% of isolates. Data is available for the years 1999 and 2000 for resistance to cefotaxime and ceftriaxone. Between 8% and 17% of *S. pneumoniae* isolates at that time had intermediate or high- level resistance to those drugs. High-level resistance in *S. pneumoniae* to cefotaxime and ceftriaxone is usually seen in those isolates that have high-level resistance to penicillin. Since the MGH study stopped in 1988, it is probable that most of the isolates of *S. pneumoniae* were penicillin susceptible. In the EDABMS, almost all of the isolates were susceptible to penicillin and were able to be treated with amoxicillin or some other penicillin derivative.

Dr. George McCracken and associates at UT Southwestern and the Children's Medical Center conducted pioneering studies leading to the conclusion that dexamethasone given before or concomitantly with ceftriaxone therapy resulted in a reduced frequency of severe hearing loss in children with *Haemophilus influenzae* meningitis. The percentage of children with a severe hearing loss was 15% in those given antibiotics alone and 3% in children given dexamethasone and ceftriaxone. The study was performed prior to 1988 and before the advent of the potent vaccine that is now available against Group B *Haemophilus influenzae* invasive disease and that has virtually eliminated this problem. Studies of the use of steroids in association with antibiotics have been performed in adults with bacterial meningitis since the 1950's. The studies usually consisted of only a small number of patients given variable amounts of steroids and many of the results could be explained by failure to stratify patients according to variables that significantly altered outcome, such as the presence of pneumonia. Because of the variability of results from these studies, there has been no consistent recommendation regarding the use of steroids in adults with bacterial meningitis. Recently, a large multi-institutional study was performed in Europe, the EDABMS, and these results are applicable to the use of steroids in adult meningitis. The study consisted of 301 adult patients enrolled mostly in the Netherlands from 1993 to 2001. The most pertinent outcome from this study is shown in Table 3. Patients given dexamethasone 15 minutes before or concomitantly with the antibiotic, overall, had a lower case fatality rate than patients given antibiotic alone. Almost all of the results for the total number of patients were accounted for by patients who had meningitis due to *S. pneumoniae*. In 50 patients with pneumococcal meningitis given

Table 3: Outcomes Eight Weeks After Admission, According to Culture Results (EDABMS)

Outcome & Culture Results	Dexamethasone Group	Placebo Group	Relative Risk (95% CI)	P Value
Death				
All patients	11/157 (7)	21/144 (15)	0.48 (0.24-0.96)	0.04
S. pneumoniae	8/58 (14)	17/50 (34)	0.41 (0.19-0.86)	0.02
N. meningitidis	2/50 (4)	1/47 (2)	1.88 (0.76-20.1)	1.00
Other bacteria	1/12 (8)	1/17 (6)	1.42 (0.10-20.5)	1.00
Negative bacterial culture	0/37	2/30 (7)	—	0.20

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placebo, 17 died for a case fatality rate of 34%. In 58 patients given dexamethasone 15 minutes before or concomitantly at the time of administration of an antibiotic, only 14% died. The relative risk was 0.41 with a 95% confidence interval of 0.19 - 0.86. The P value was highly significant at a level of 0.02. Note that the placebo group had a 34% case fatality rate which is identical to the case fatality rate of patients with *pneumococcal meningitis* at MGH (28%) and at PMH (35%). The dose of dexamethasone utilized was 10 mg q6H for a total of 4 days. Note that in the EDABMS in the *Neisseria meningitidis* group, the case fatality rate was lower than in the MGH study (15%) and that there was no effect of dexamethasone on mortality even though 97 patients were included in the EDABMS. No effects were observed in the group with other bacteria and in those having a negative bacterial culture. The results of this study indicate that in this large series of patients, the use of dexamethasone before or concomitantly with the administration of antibiotics lowered the case fatality rate from

34% to 14% in *pneumococcal* meningitis and this difference was highly statistically significant. In patients with etiologies other than the pneumococcus, there was no effect. The results in the *S. pneumoniae* group were sufficient to alter the effect for all patients so that for the total there was a statistically significant difference. In this study, almost all patients with *S. pneumoniae* meningitis had penicillin susceptible isolates. Adverse events in the EDABMS were not different between the dexamethasone and the placebo groups (Table 4). There was no difference in the occurrence of gastrointestinal bleeding, hyperglycemia, herpes zoster or a fungal suprainfection. There was

Table 4: Adverse Events (EDABMS)

Event	Dexamethasone Group (N=157)	Placebo Group (N=144)	P Value
	no. (%)		
Gastrointestinal bleeding	2 (1)	5 (3)	0.27
Blood transfusion required	2 (1)	4 (3)	0.43
Stomach perforation	1 (1)	0	1.00
Hyperglycemia	50 (32)	37 (26)	0.24
Herpes zoster	6 (4)	4 (3)	0.75
Fungal infection	8 (5)	4 (3)	0.38

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difference in the severity of gastrointestinal bleeding between the two groups in terms of the numbers of patients that required a blood transfusion or those who had a gastric perforation. Although the authors of the EDABMS conclude that their results are applicable to all adults with bacterial meningitis, the editorialists commenting on the

study and others conclude that their results are presently applicable only to patients with pneumococcal meningitis, would not advise treating patients with dexamethasone for other bacterial etiologies and would discontinue the drug when it became evident that the pneumococcus was not involved in the etiology of the meningitis.

The etiologies of bacterial meningitis following trauma or surgery at PMH or nosocomial acquisition at MGH are compared (Table 5). *S. aureus* accounted

Table 5: Etiologies of Purulent Meningitis Following Trauma or Surgery (PMH) or Nosocomial Acquisition (MGH)

	PMH 1980-1999	MGH 1962-1988
Cases	**56**	**151**
% of Cases		
S. aureus	27	9
Coagulase negative staphylococci	14	9
Streptococci	7	9
Enterococcus	5	3
Gram negative bacilli	39	38
Mixed bacterial species	7	7
Other	3	25

PMH data. MGH data from Durand et al. Vol. 328, No. 1

for 9% of cases at MGH and 27% of cases at PMH. Coagulase negative staphylococci accounted for between 9% and 14% of cases, streptococci between 7% and 9% of cases, enterococcus between 3% and 5% of cases and gram-negative bacterial species accounted for 38% and 39% of cases. In the MGH series, other organisms accounted for approximately 25% of cases and included *S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, *H. influenzae* and 11% of cases in which no culture was positive. This

group of patients represents a heterogeneous mix. Some of the cases are young and meningitis is discovered early because they are in the hospital. Although most of the organisms tended to be resistant, antibiotics, for the most part, are able to manage the infection adequately. Other patients in this group have serious underlying diseases like subarachnoid hemorrhages or tumors and the meningitis acts as a terminal event. Empiric antibiotic therapy in bacterial meningitis on the Medicine service usually consists of vancomycin at dosages of 50 mg per kilogram up to 4 grams per day plus cefotaxime or ceftriaxone plus or minus ampicillin since cefotaxime and ceftriaxone do not cover *Listeria monocytogenes* and there have been failures of vancomycin therapy in Listeria infections. For neurosurgery, vancomycin plus cefepime is recommended. Meropenem is under investigation. Dexamethasone therapy is now recommended for pneumococcal meningitis. It is not recommended at the present time for other etiologies of bacterial meningitis or of bacterial meningitis that should occur following trauma or after surgery.

It is presently debated to what extent should patients with suspected meningitis undergo CT scanning of the head before a lumbar puncture. If CT scanning of the head is done, blood cultures should be drawn immediately and the patient should be started on empiric antibiotics before awaiting the results of the CT scan and a subsequent lumbar puncture. Awaiting the results of these procedures may delay therapy and be potentially deleterious to the patient. In the MGH series, autopsy records were available from 27 of 40 patients with community-acquired meningitis who died within 7 days of presentation and 8 had evidence of herniation. In 5, clinical signs of herniation developed within a period ranging from several minutes to several hours after the

lumbar puncture. Opening pressures were recorded for 4 patients and were all greater than 500 millimeters of water. A study delineating the factors which might predict an abnormal CT scan in adults with suspected meningitis was recently performed at the Yale-New Haven Hospital (Table 7). The investigators studied 235 adults with

Table 7: Results of CT of the Head in 235 Adults with Suspected Meningitis

Result	No. of Patients (%)
Normal	179 (76)
Abnormal	56 (24)
Focal lesion without mass effect	29 (12)
Nonfocal lesion without mass effect	12 (5)
Focal lesion with mass effect	9 (4)
Nonfocal lesion with mild mass effect	2 (1)
Combinations of focal and nonfocal lesions without mass effect	4 (2)

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suspected meningitis and found a normal CT scan in 76% and an abnormal CT scan in 24% with 5% of patients showing a mass effect. They delineated characteristics predictive of a normal CT scan, thus, potentially obviating the need for CT scanning before lumbar puncture. The characteristics consisted of age at least 60 years, an immunocompromised state, a history of a central nervous disease, seizure within one week before presentation and the following abnormalities: abnormal level of consciousness, inability to answer 2 consecutive questions correctly, inability to follow two consecutive commands correctly, gaze palsy, abnormal visual fields, facial palsy,

arm drift, leg drift and abnormal language. Patients were grouped into those persons who had an absence of any of these base-line characteristics as opposed to those persons who had the presence of any base-line characteristic. Patients who had none of those characteristics had a 97% probability of having a normal CT scan (Table 8).

Table 8: Identification of the Subgroup of Adults with Suspected Meningitis Who have a Decreased Likelihood of having Abnormal Findings on CT of the Head

Presence of Any Base-Line Characteristic	Result on CT of the Head		
	Normal	Abnormal	Total
	no. of patients %		
No	93 (97)	3 (3)	96 (100)
Yes	86 (62)	53 (38)	139 (100)
Total	179 (76)	56 (24)	235 (100)

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Only 3 patients without any of the delineated base-line characteristics had an abnormal CT scan. Presence of any of the base-line characteristics resulted in an increased number of patients having an abnormal CT scan. Performing these clinical measurements upon first entrance into the emergency department, it is possible to predict that 41% of patients with suspected meningitis would have a 97% chance of having a normal CT scan and, thus, obviate the necessity for performing the CT scan before doing a lumbar puncture in these patients. The presence of any of these abnormalities led to the action of doing a CT scan followed by a lumbar puncture if a

significant mass effect could be excluded. In the Yale-New Haven Hospital study, evaluation of venous congestion in the eye or papilledema was not attempted because it was considered improbable that the skills necessary to perform this exam would be uniformly distributed among the physicians who might be seeing patients in the usual emergency department.

Drug-induced Aseptic Meningitis

Case

The patient is a 20-year-old woman who has dermatomyositis diagnosed in 2001 when she presented with fatigue, joint-pain, rash and proximal muscle weakness. She was placed on 60 mg prednisone per day but this was discontinued 3 months prior to admission. On August 11, 2003, because of a flare of her disease, she was given IVIG. The dose was repeated on August 12. Shortly after the infusion, she developed a frontal headache, nausea and vomiting, chills, fever and photophobia. She was hospitalized on August 13 and started on antibiotics (vancomycin, cefotaxime and ampicillin). When CSF cultures were negative on day 2, she was continued on cefotaxime to complete a 10-day course. Two LPs were performed:

	8/13	8/17
CSF glucose	41	51
CSF protein	203	22
Tube #4		
No. nucleated cells	1045	15
RBCs	8	98
% PMNs	82	3
% Ls	3	30
% Ms	15	23
% Es		43
% Bs		1
Presence of reactive Ls		+

This patient presented with a convincing history and clinical findings that she had drug-induced aseptic meningitis (DIAM) after exposure to IVIG. Shortly after the second infusion of IVIG, she developed manifestations consistent with meningitis. On the subsequent day she was hospitalized. Lumbar puncture revealed a large number of nucleated cells, most of which were polymorphonuclear leukocytes. The CSF glucose was normal but the CSF protein was elevated. Four days later, the number of nucleated cells in the CSF had decreased to 15 and there were 43% eosinophils. There were also reactive lymphocytes present in the CSF. Bacterial cultures were negative. Drug-induced aseptic meningitis with IVIG therapy has been reviewed. The CSF characteristics were reviewed in 5 patients, 3 of which are depicted (Table 9). The leukocyte count always elevated with an increased percent of polymorphonuclear

Table 9: DIAM with MG Therapy

	Erythrocyte Count	Leukocyte Count	Polymorpho-Nuclear Neutrophils	Lympho-cytes	Eosino-phils	Glucose Concen-tration	Protein Concen-tration	IgG
y		X10 ^{6}/L	←	%	→	mmol/L	← g/L	→
1 M,40	0.0	752.0	87	7	1	3.16	.063	0.14
	6.0	453.0	46	37	3	3.44	0.31	0.07
2 M, 7	558.0	222.0	85	11	0	3.11	0.34	0.05
3 M,37	9.0	1169.0	85	5	1	3.66	1.0	.22

Sekul et al. Ann IM 121(4): 259

leukocytes. The glucose concentration was normal but the protein concentration was usually elevated. Studies delineating whether the CSF protein is derived from the IVIG have not been performed. Other drugs including NSAIDs, antibiotics and OKT3 have also been shown to be associated with drug-induced aseptic meningitis. Patients with systemic lupus erythematosus have an increased chance of having aseptic meningitis if given a drug. The clinical signs and symptoms of patients with drug-induced aseptic meningitis are shown (Table 10). The symptoms and signs are depicted in terms of decreasing incidence. Note that in addition to meningitis, some patients have findings indicative of more deep- seated cerebral dysfunction such as abnormal consciousness or a focal neurological deficit. In addition to IVIG and OKT3, the NSAIDs and antibiotics involved in DAIM have been catalogued (Tables 11 and 12). With NSAIDs,

Table 10: Clinical Signs and Symptoms of Patients with Drug-Induced Aseptic Meningitis

	Patient Groups, %					
	NSAID	Antibiotics	IVIG	OKT3	SLE	Total
Fever	94	96	92	68	90	86%
Headache	78	89	96	65	85	79%
Meningeal signs	72	86	89	43	80	70%
Arthomyalgias	22	21	–	19	30	54%
Nausea and/or vomiting	60	64	86	22	70	53%
Abnormal consciousness	50	64	23	59	50	50%
Photophobia	–	–	34	32	10	32%
Facial edema	25	21	–	–	20	24%
Focal neurologic deficit	16	11	–	20	10	18%
Rash	22	10	–	5	35	12%

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Table 11: Drugs Involved in Drug-Induced Aseptic Meningitis

Drug Group	No. of Reported Cases	Drugs Involved (No. of Cases)	% of Females	Age, Mean ± SD (Range), y	Range of Latency (Median)	Prior Exposure to Drug
NSAIDs	43	Ibuprofen (32)	67	37±15 (21-73)	30 min to 4 mo (4h)	45
		Tolmetin (1)				
		Sulindac (5)				
		Naproxen (2)				
		Diclofenac sodium (1)				
		Ketoprofen (1)				
Antibiotics	39	Sulfamethizole (1)	78	44±20 (6-82)	10 min to 10 d (3h)	35
		TMP-SMX (20				
		TMP (10)				
		Isoniazid (1)				
		Ciprofloxacin (1)				
		Penicillin (1)				
		Metronidazole (2)				
		Cephalosporin (1)				
		Pyrazinamide (1)				
		Sulfisoxazole (1)				

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Table 12: Drugs Involved in Drug-Induced Aseptic Meningitis

Drug Group	No. of Reported Cases	Drugs Involved (No. of Cases)	% of Females	Age, Mean ± SD (Range), y	Range of Latency (Median)	Prior Exposure to Drug
IVIGs	33 (0%-7%)		45	20±17 (2-62)	10h to 8d (36h)	35
OKT3	39 (1%-7%, 5%)		57	37±17 (7-62)	3h to 7d (72h)	3
SLE group	22	Ibuprofen (14)	90	38±14 (21-73)	20 min to 2 wk (4h)	50
		Tolmetin (1)				
		Sulindac (1)				
		Naproxen (1)				
		Diclofenac sodium (1)				
		TMP-SMX (2)				
		TMP (1)				
		Sulfisoxazole (1)				

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ibuprofen is the most common drug. With antibiotics, sulfatrimethoprim is the most common implicated drug. Most of the patients have had a prior exposure to the drug and the median time of exposure to the drug to the development of symptoms is usually within 3-4 hours. Patients with SLE have a tendency to develop DIAM when given drugs, the most common agent being ibuprofen. Drug-induced aseptic meningitis has to be suspected when the patient presents with aseptic meningitis following the ingestion of a drug. Many of these patients have an underlying connective tissue disease. The CSF findings suggest aseptic meningitis except that initially there is a predominance of polymorphonuclear leukocytes. Occasionally a patient will present with an eosinophilic meningitis, and in our case on the second lumbar puncture, the patient had 43% eosinophils. Unless the condition has occurred previously, it is difficult to exclude bacterial meningitis and many of these patients are treated with a 10-day course of cefotaxime or ceftriaxone. In the patient presented in this section, she

became asymptomatic shortly after entering into the hospital. The second lumbar puncture showed a marked diminution in the number of cells and a pronounced eosinophilia. Challenge studies with the offending drug are sometimes performed to establish the diagnosis for certain. In this patient, no challenge was made but the managing physicians were made aware of the presumptive diagnosis.

Mollaret's Meningitis

Case

Within 2 years, this 32-year-old man had 4 episodes of meningitis. The first two episodes were treated with intravenous ceftriaxone. He was not treated for the second two episodes, which were thought after CSF examination, to represent aseptic meningitis. He has had a negative MRI of the head, cannot relate any of the episodes to ingestion of a drug and denies outbreaks of orolabial and genital herpes. Before his first episode of meningitis, he began having sex with a new partner. She denies having oral and genital herpes but does state that she occasionally notes painful areas or lacerations on her labia.

Mollaret's meningitis was described in 1944 by Mollaret in France (Table 13). The differential diagnosis includes the presence of a cyst with intermittent rupture, CSF leaks and bacterial meningitis and drugs (DIAM). If these entities can be excluded from consideration, there is now information that indicates that the most common pathogen involved in Mollaret's meningitis is herpes simplex virus. Herpes simplex virus type 2 is considered to be the predominant pathogen as opposed to herpes simplex virus type 1.

Table 13: Mollaret's Meningitis

- First described in 1944
- Differential diagnosis includes cyst rupture, CSF leaks, drugs
- Mollaret cell is an activated monocyte
- During episodes, there is increased IgG, IL6, TNF alpha and PGE2 in CSF
- In the early part of the episode, HSV DNA may be present in CSF. HSV-2 >> HSV-1
- If due to HSV, prophylactic acyclovir may prevent further episodes

Five patients with Mollaret's meningitis are presented (Table 14). Note that they have aseptic meningitis with an increased number of mononuclear cells in the CSF,

Table 14: Selected Clinical Data for Study Patients

Patient	Age, Sex	Leukocyte Count and Differential	CSF Glucose	CSF Protein	CSF Antibody	HSV DNA Type	Attacks	Years	Average Duration
		μL	*mmol/L*	*g/L*			*n*		*d*
1	26,F	1600 (98 L, 2 PMN)	2.66	1.35	HSV-2	HSV-2	4	4	3 to 5
2	41,M	375 (86 L, 5 M, 9 PMN)	2.61	1.07	HSV-2,	HSV-2	5	9	4 to 5
3	43,F	417 (74 L, 22 M, 4 PMN)	2.28	2.40	HSV-2	HSV-2	3	2	3 to 10
4	42,M	390 (81 L, 15 M, 4 PMN)	3.16	0.93	HSV-2	HSV-2	4	8	10 to 14
7	32,F	48 (58 L, 42 PMN)	3.00	1.04	HSV-1	HSV-1	9	8	3 to 5

Fedder et al. Ann IM 121(5): 334

normal CSF glucose concentrations and elevated protein concentrations. Many of them have had multiple episodes over a period of time with the average duration of the episode lasting from 3-14 days. In the patients presented in this series, HSV-2 DNA was usually but not always found in the CSF by PCR. Concentrations of specific HSV antibody in the CSF were elevated implying direct manufacture of immunoglobulin locally by cells in the CSF. Critical to the establishment of a diagnosis of Mollaret's meningitis is to have HSV DNA measured in the CSF of patients early in the course of one of their recurrent episodes. Many of the patients with recurrent aseptic meningitis do not have genital lesions at the time of presentation and a critical issue is to ascertain whether there has been exposure to HSV-2. Type specific HSV serology is now available, is FDA approved and can help in the work-up of patients who have recurrent meningitis (Table 15). These tests detect antibodies to specific viral surface

Table 15: HSV Type Specific Serology

- New tests (EIA and WB) can detect antibody specific for HSV-1 and HSV-2
- These tests detect antibody against surface glycoproteins unique to HSV–1 (gG1) or HSV-2 (gG2)
- FDA approved
- Presently debated on how these tests may be used but they may help in managing patients with atypical genital syndromes or Mollaret's meningitis

glycoproteins that are unique to HSV-1 or HSV-2. They utilize either EIA or Western blot formats. It is presently debated on how these tests may be used but they may help in managing patients with atypical genital syndromes or Mollaret's meningitis. At the Mayo Clinic Clinical Microbiology Laboratory, 249 patients were found to have a CSF positive for HSV DNA by PCR (Table 16). Seventy-eight of the 117 patients from

Table 16: HSV DNA in CSF

- At Mayo Clinic Clinical Microbiology Laboratory, 249 patients were found to have CSF positive for HSV DNA by PCR (Jan., 1999- Aug., 2000)
- Identifying data were available from 117 of these patients
- 39 patients had HSV-1 DNA (89% had encephalitis)
- 78 patients had HSV-2 DNA (most had meningitis)
  - Only 7% (5/69) had concomitant genital herpes
  - Of 27 patients with recurrent meningitis, none had active genital herpes at presentation

O'Sullivan et al. Mayo Clin. Proc. Vol. 78, 2003

whom identifying data were available had HSV-2 DNA in the CSF and most had meningitis. Twenty-seven of these patients had recurrent meningitis but none of them had active genital herpes at the time of presentation.

Type specific HSV EIA tests were performed on the patient. His type specific EIA test for HSV-1 antibody was 0.4 (negative <1) the HSV-2 EIA test is 5.0. His partner's type specific HSV-1 EIA was 2.3 and her type specific HSV-2 EIA test value was 3.2. A reasonable hypothesis is that he may have become infected with HSV-2

prior to his first episode of aseptic meningitis and that this episode was not associated with genital herpetic lesions. He has never had genital herpes. One possible way of managing such a patient is to place him on a prophylactic dose of acyclovir or valacyclovir to determine whether he would remain free of further episodes of meningitis.

The Etiology of Encephalitis

A major study has been performed in California by Glaser and colleagues who studied 334 patients with clinical encephalitis or encephalopathy who were over the age of 6 months. They were studied during the period 1998-2000 (Tables 17-18). For the

Table 17: California Encephalitis Project

- Encephalitis, encephalopathy 1998-2000, age > 6 months
- 334 patients enrolled
  - Confirmed or probable 42 (13%)
    - Virus 31 (9%)
    - Bacteria 9 (3%)
    - Parasite 2 (1%)
  - Possible 41 (12%)
  - Non-infectious etiology 32 (10%)
  - Non-encephalitis infection 11 (3%)
  - Undetermined etiology 208 (62%)

Glaser et al. CID 36(6): 731

Table 18: California Encephalitis Project

➢42 (13%) confirmed or probable / 41 (12%) possible

•Viral 55			
- HSV-1	11/3	Rotavirus	2/0
- VZV	3/1	Rabies	1/0
- EBV	4/0	Influenza A	0/1
- HHV-6	1/1	Influenza B	0/1
- Enterovirus	5/13	Adenovirus	0/2
- Measles (SSPE)	2/0	Parainfluenza	0/1
- Hepatitis C	2/0	RSV	0/1
•Bacterial or parasitic 28			
- *M. pneumoniae*	2/9		
- *B. henselae*	7/0		
- Brucella sp.	0/2		
- Chlamydia sp.	0/6		
- *Baylisascaris procyonis*	2/0		

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334 patients that were enrolled, 42 had a confirmed or probable etiology (13%) and 41 (12%) had a possible etiology diagnosed. In 32 patients (10%), a non-infectious etiology was ascertained, like exposure to a toxin. Eleven (3%) had non-encephalitis infection. A couple of these latter patients had tuberculous meningitis. In 208 (62%) of the patients, despite extensive testing with the most modern technologies and all the antigens that were available, no etiology was able to be ascertained. Of the 42 who had a confirmed or probable etiology and the 41 who had a possible etiology, herpes simplex virus type 1 accounted for 14 (11/3) cases, enteroviruses for 18 (5/13) cases and a variety of other viruses including VZV (3/1), EBV (4/0) and others caused the rest. Bacterial or parasitic disease was responsible for 28 cases with *Mycoplasma pneumoniae* (2/9) and *Bartonella henselae* (7/0) accounting for the majority of cases. One parasite, the raccoon roundworm, *Baylisascaris procyonis*, accounted for 2 cases. Note that in this particular study, arboviruses were not involved in any of the cases.

This represents an unusual experience for California in that Western equine encephalitis virus and St. Louis encephalitis virus usually cause cases of encephalitis in that state. The study period was too early in the West Nile epidemic to have had any cases of West Nile virus encephalitis.

In Dallas at the Medical Center in a retrospective study involving patients from Parkland and Zale Lipshy University Hospital from June 1994 through the end of May 1999, 29 adults were found to have encephalitis, 26 at Parkland and 3 at Zale. There were no cases of herpes simplex encephalitis, 11 of St. Louis encephalitis, 2 related to varicella-zoster virus and 1 to cytomegalovirus. Fifteen of the cases, however, had no known etiology. No immunosuppressed patients were studied. In a prospective study from March 2001 to December 2002 at Parkland, Zale and Children's Medical Center Cloud, Hardy and Koo found 18 patients with encephalitis who were not immunosuppressed. One of these patients had herpes simplex encephalitis, 6 had West Nile virus encephalitis but 11 had an unknown etiology. Of the 11 with an unknown etiology, 8/8 that were tested for CSF HSV DNA by PCR had negative studies. In 2 separate studies, patients with encephalitis were found at UT Southwestern University hospitals; 26 of these patients (55%) had encephalitis of unknown etiology even though most of them had appropriate studies for the majority of known pathogens.

With regard to the diagnosis of encephalitis, demonstration of the pathogen by culture, PCR or pathology is always considered the most specific test. If the patient can be shown to have specific IgM antibody in the CSF that indicates a recent infection, it is usually diagnostic. For IgG antibody in the CSF to be significant, there must be a correction for passive diffusion. This correction for passive diffusion is usually made by

calculation of the virus antibody index and the formula for the calculation of this value is given (Table 20).

Table 20: Virus Specific CSF Antibody

- Presence of specific IgM in CSF evidence of recent infection
- For IgG, there must be a correction for passive diffusion
  - 100 antibody units in serum can result in 1 antibody unit in CSF
  - Virus ab index $= \dfrac{\dfrac{\text{CSF virus ab titer}}{\text{CSF albumin or IgG}}}{\dfrac{\text{Serum virus ab titer}}{\text{Serum albumin or IgG}}}$
  - Using albumin as correction factor, a CSF virus ab index ≥1.9 suggests local manufacture of IgG ab in CSF
  - Using IgG, a positive value ≥1.5
  - CSF virus antibody index may be low or negative initially and increases with duration of infection. It can remain elevated for an extended duration.

This formula accounts for the passive diffusion of antibody into the CSF by a correction factor usually using albumin or IgG and their relative concentrations in the serum and CSF. The CSF virus antibody index may be low or negative initially in the course of infection. It does increase with the duration of infection and it can remain elevated for an extended time.

Specific Causes of Encephalitis

The most common sporadic form of encephalitis in the world is herpes simplex encephalitis. This disease process usually represents reactivation of HSV rather than primary infection. In reactivation disease, temporal lobe localization is usual with HSV-1 predominating as the pathogen. The anatomic position of latency of HSV-1 is the

trigeminal ganglion and it is postulated that HSV-1 reactivates and then can reach the meninges underling the temporal lobe. The virus then passes into the temporal lobe where it causes an asymmetric hemorrhagic encephalitis, which extends into the fronto-parietal lobes. The diagnosis is best established by a positive PCR for HSV DNA in the CSF. One can also make the diagnosis by positive and rising HSV CSF antibody index values. In cases of herpes simplex encephalitis, the first lumbar puncture may yield false negative results. The brain biopsy was formally considered the gold standard for diagnosis and it should still be considered in the work-up of patients with temporal lobe lesions if the PCR and CSF antibody indices remain negative. Therapy consists of acyclovir for a 14-day period of time; the therapy can be extended depending upon the clinical course of the patient and whether the PCR is positive for HSV DNA at 10-12 days after therapy has been instituted. Dexamethasone can be administered for cerebral edema as needed. The prognosis has been found to be related to the severity of the illness at admission into the hospital and to a delay (> 2 days), in receiving acyclovir between admission and the time of institution of the drug.

Herpes simplex encephalitis can occur in neonates. It can also occur as a primary infection which is more common in children. Temporal lobe localization still tends to be usual but other sites of localization may occur and it is conceived that the virus may make its way into the central nervous system by hematogenous spread from the original site of infection which is probably the oropharynx. Since herpes simplex virus is a cytocidal virus causing acute inflammation, cell damage or death, MR can usually spot these areas of encephalitis by showing focal expanding areas of edema that enhance with contrast. If PCR of the CSF is used as the primary diagnostic

modality, does localization always occur in herpes simplex encephalitis? The MRI is the most sensitive test for localization but the first study may be negative. In the California encephalitis project, 14/14 cases of herpes simplex encephalitis had localizing abnormalities. In one series of 93 patients (the French prognosis study), parietal (6) and occipital localization (2) occurred without temporal localization and there was no evidence of localization in 2 patients. Series and case reports suggest atypical areas of localization including the brain stem, the cerebellum and the occurrence of transverse myelitis. There is 1 case report of cognitive changes and no localization early in the course of a patient with CLL (HSV-2). Two of 24 patients with herpes simplex encephalitis diagnosed by PCR were reported to have no localizing features (University of Colorado series).

Varicella-zoster virus can cause CNS infection (Table 21). It usually causes cerebellitis as a post-infectious event in varicella. It can be associated with herpes

Table 21: CNS Infection Due to Varicella-Zoster Virus

- Cerebellitis as a post-infectious event (varicella)
- Association with varicella, herpes zoster or zoster without an eruption
  - Diagnosis by PCR or VZV CSF ab index
- Granulomatous large vessel vasculitis
- AIDS
  - PCR positivity in CSF
    - Clinical manifestations and response to therapy
    - No clinical manifestations
  - In advanced disease there can be a small vessel vasculopathy with infarcts
    - PCR
    - VZV CSF Ab index
    - Response to therapy

zoster or zoster without an eruption. It can cause granulomatous large vessel vasculitis and contralateral hemiparesis. Of pertinence now in patients with AIDS and advanced disease, there may be a new entity wherein these patients may have a small vessel vasculopathy with infarcts, which have a characteristic MR appearance. They have CSF tests that are positive for VZV DNA by PCR or they have an antibody index for varicella-zoster virus that is elevated. Patients with small vessel vasculopathy may improve with specific antiviral chemotherapy.

The two most important arboviruses that produce encephalitis in Dallas are St. Louis encephalitis (St.LE) virus and West Nile virus (WNV). St. Louis encephalitis virus has caused Dallas epidemics in 1966, 1976 and 1995. The 1996 epidemic occurred in the setting of a rudimentary mosquito control program and resulted in 168 laboratory-documented cases. Aerial spraying was necessitated to control the epidemic. The age specific incidence of disease due to this viral infection rises with age. Tremors are common in this illness and are seen in at least 60% of patients. Frank paralysis is rare. In 2/7 immunologically normal patients studied by MR, edema was seen in the substantia nigra bilaterally. These patients had striking tremulousness along with other extrapyramidal signs. St. Louis encephalitis virus is antigenically relayed to West Nile virus and in Dallas in order to make specific etiological diagnosis; virus antibody studies must be performed utilizing antigens from both of these agents.

Of recent major import is the occurrence of West Nile virus encephalitis in the United States (Table 22). In Dallas in 2002 it accounted for 25 cases and in 2003, 50

Table 22: West Nile Virus Disease in the United States, 1999-2003

Variable	1999	2000	2001	2002	2003
			n		
States with documented animal infection	4	12	27	44	47
States with human infection	1	7	10	40	46
Cases of West Nile virus	66	21	62	4156	9122
Deaths	9	2		284	223

cases were involved. In 2002, 6 cases were seen at Parkland whereas 22 cases were seen in 2003. West Nile virus is a flavivirus related to dengue virus, St. Louis encephalitis virus and Japanese encephalitis virus. It was isolated first in 1937 by Smithburn from the blood of a woman who presented with the febrile illness in the West Nile district of Uganda. Except for the dengue viruses, West Nile virus is the most geographically widespread arbovirus. It occurs in South Africa, throughout the Middle East, into southern Russia and into Eastern Europe. In 1999 it was introduced into North America. Prior to 1996 the virus mostly caused a febrile illness with rash, lymphadenopathy, pharyngitis and occasionally pancreatitis, hepatitis or myocarditis. Investigators in Israel noted the occurrence of central nervous system disease but it occurred only in a minority of patients. In 1996 a new event occurred. In Bucharest,

Romania there was a large epidemic involving 393 laboratory-documented cases with most having central nervous system involvement. The epidemic involved mostly elderly patients and the overall case fatality rate was approximately 5%. In 1999 a large epidemic occurred in Volvograd, Russia. This epidemic again involved elderly persons and most had central nervous disease. In 1999 West Nile virus was introduced into the northeastern United States with an epidemic involving New York City. The New York City virus was shown to be closely related to a 1998 Israeli goose isolate. West Nile virus has now occurred throughout the United States with the exception of a few states on the western coast. There have been genotypic and phenotypic changes in the virus that have resulted in its increasing neurovirulence and its capacity to cause disease predominantly in older individuals. It also has the capacity to cause bird deaths, particularly in crows and blue jays. It can infect and cause death in horses. Through 2003, 46 of the 50 states in the United States have had West Nile virus activity and in 2003 there were 9,122 cases including 223 deaths. In 2002 and 2003, West Nile virus caused the largest arborviral epidemics ever seen in the United States except for dengue virus. St. Louis encephalitis virus caused a major epidemic in 1975 resulting in at least 2,000 laboratory-confirmed cases.

A present debate revolves around how many infections there are for each clinical case and what is the proportion of cases with the febrile illness as opposed to cases with significant central nervous system involvement (encephalitis, aseptic meningitis, flaccid paralysis) (Table 23). In the 1999 New York City epidemic, it was thought that

Table 23: WNV: Spectrum of Infection and Disease

- 1999 NYC epidemic
  - Fever 1/5 infected
  - Severe neurologic disease 1/150 infected
- 2002
  - Overall clinical case/ inapparent infection ratio approximates 1/150-1/250
  - Cases
    - Fever 25-30%
    - CNS disease (encephalitis, meningitis) 70-75%
    - Overall case-fatality rate 5-10%
- 2003
  - Cases
    - Fever 70%
    - CNS disease 30%

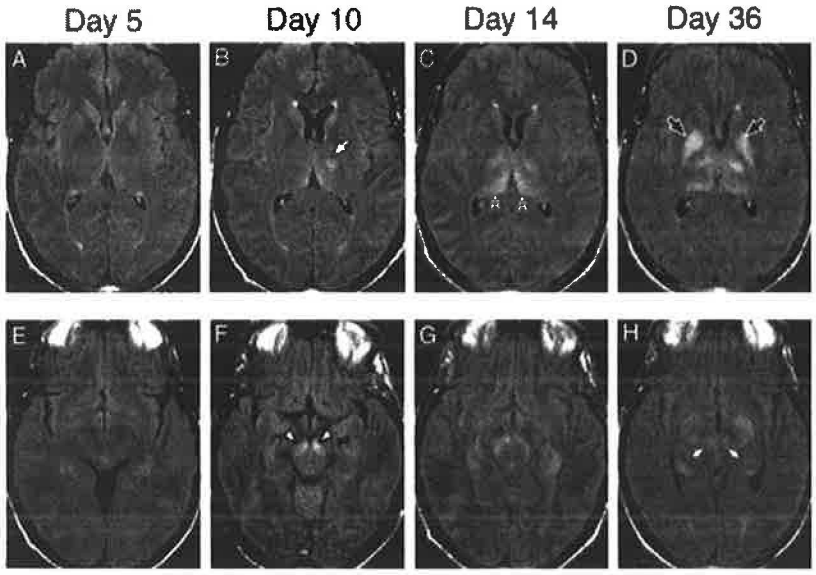
fever occurred in 1/5 who were infected and severe neurologic disease occurred in 1/150 infected persons. In 2002, surveillance sponsored by CDC revealed that the clinical case to apparent infection ratio approximated 1/150 to 1/250. 25-30% of the cases had a febrile illness whereas central nervous system disease occurred in 70-75% of the human cases. In 2003, more cases of patients with the febrile illness (70% of cases) were seen as opposed to cases with central nervous system disease (30%). This was particularly apparent in Colorado where there were more than 2,300 clinical cases. Most of the Colorado cases involved the vector mosquito *Culex tarsalis.* This is the major rural vector of St. Louis encephalitis and Western equine encephalitis. Where this mosquito is vector, epidemics of St.LE are not associated with an increasing age incidence. Exposure may be the primary variable. The epidemiology of WNV involves infection of a bird, which then develops viremia of sufficient magnitude to infect other mosquitoes taking a blood meal. Birds can have viremia of such a high magnitude that

they die from their infection. Humans usually are asymptomatically infected but certain persons develop disease, particularly elderly persons and perhaps patients who may be immunosuppressed. Humans are thought to be a dead-end in the transmission cycle. However, they have been responsible for some cases of disease because of blood donations given when asymptomatic and during the incubation period of the disease. In Dallas in 2003, as many as 10 units per 10,000 tested during the summertime were found to be positive by PCR for West Nile virus. Organ transplantation has been associated with West Nile virus transmission. The donor may have developed infection by blood transfusion or through a mosquito bite. Since the recipient(s) of the organ(s) may be immunosuppressed, illness in these patients can be severe. There is at least one report of transplacental WNV transmission with the development of fetal abnormalities. Breast feeding has resulted in the asymptomatic transmission of the virus in at least one case. Occupational exposure and infection occurs with the virus in laboratory workers.

West Nile fever is characterized by an incubation period of 2-15 days followed by fever, myalgias, headache, nausea and vomiting. There may be a rash and lymphadenopathy. The patient may be leukopenic and rarely have pancreatitis, hepatitis or myocarditis. With central nervous system disease, they can have aseptic meningitis which tends to be much more infrequent than encephalitis. With encephalitis, there is a disturbance in cerebral function. A characteristic feature of these patients is that some of them develop flaccid paralysis related to anterior horn cell damage due to viral infection. Occasional patients just have flaccid paralysis. In some patients tremors may occur and they can have findings suggesting Parkinsonism. They

can be hyponatremic presumably on the basis of SIADH. Rhabdomyolysis can be initiated by the viral infection. There is one patient reported who developed central diabetes insipidus. The virus has involved the eye in a number of cases and, in one patient, blindness was reported due to optic neuritis and chorioretinitis. MR imaging and the CNS pathology are of interest. Neuroimaging by MR in heavily immunosuppressed and/or elderly patients has shown lesions predominantly in the basal ganglia, the thalamus, the pons, the substantia nigra, the globus pallidus and the red nuclei (Figure 1). These lesions represent edema and are seen on T2 and flair

Figure 1: Progression of West Nile Virus Encephalitis in Deep Gray Nuclei



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sequences and do not enhance with contrast. They are infrequent being seen only in immunosuppressed patients or a few elderly persons. In 2/7 immunologically normal patients with St. Louis encephalitis the substantia nigra alone showed edema. By histopathology, West Nile virus is mainly detected in structures around the neuroaxis,

namely in the thalamus, the brain stem, the basal ganglia, deep brain nuclei and the substantia nigra. It can also be detected in the spinal cord and in the cerebellum.

The diagnosis of West Nile virus disease can be made by PCR early in the course of illness (Table 24). Most patients with West Nile virus disease have IgM

Table 24: Laboratory Diagnosis

- Compatible clinical case
- Virus isolation (culture or PCR)
- Four-fold rise in antibody titer
- Presence of IgM antibody in serum and CSM
- Presence of IgM antibody in CSF
- Presence of IgM antibody in serum (evidence of a probable case)

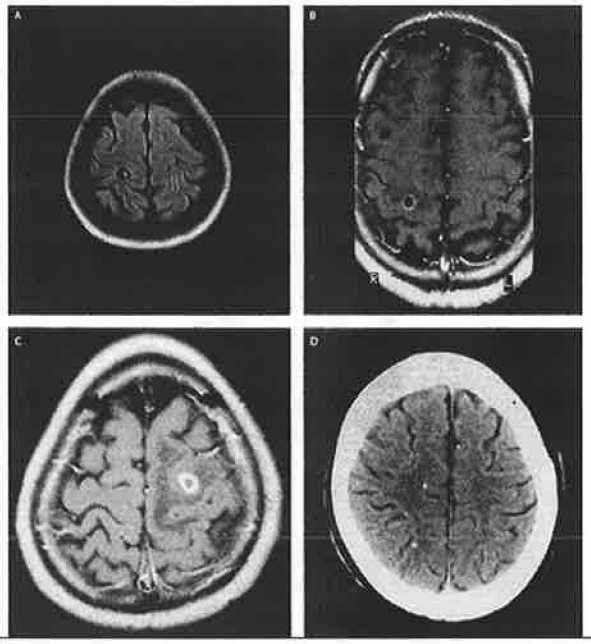
antibody present in serum at the time of admission into the hospital, they usually also have IgM antibody in the CSF at that time. If CSF IgM antibody is not present initially, it may be positive one or two days later. Serum WNV IgM antibody can remain elevated for as long as two years after infection. However, CSF WNV IgM antibody lasts only for about 50 days and the presence of both serum and CSF IgM usually indicate a recent infection. Diagnosis can usually be established within a short period of time after receipt of the appropriate specimens into the hospital laboratory. Diagnosis usually is done by a capture IgM EIA test performed on the CSF and the serum. An immunofluorescence antibody test can also be performed and is only slightly less

sensitive than the capture IgM EIA test. In immunosuppressed persons, IgM antibody may not be formed early in the course of illness and in order to make a diagnosis in these persons, PCR should be utilized. The long-term prognosis of West Nile virus infections is usually good. There may be persistent headaches and abnormalities in concentration and memory difficulties. There may be exceptional overwhelming fatigue but usually people recover. It remains to be determined how many patients experiencing flaccid paralysis improve and at to what extent. Experimental therapeutic options in West Nile disease include interferon alpha and West Nile virus hyperimmune serum globulin. These modalities are presently undergoing active investigation. Considered but ruled out as therapeutic possibilities are ribavirin and steroids.

Neurocysticcarcosis

A double-blinded study was performed in Peru assessing specific anti-neurocysticercosis chemotherapy and steroids as opposed to treatment of the patients with a double placebo. The 2 arms of the trial compared albendazole 400 mg twice a day and 6 mg dexamethasone daily for a 10-day period of time opposed to a double placebo. Only patients with active cysts were included in the study and the presence of the active cyst had to be ascertained by CT or MR imaging. People with inactive cysts, mostly patients with calcified granulomas, were excluded from the study (Figure 2).

Figure 3: Stages of Neurocysticercosis Lesions in the Human Brain



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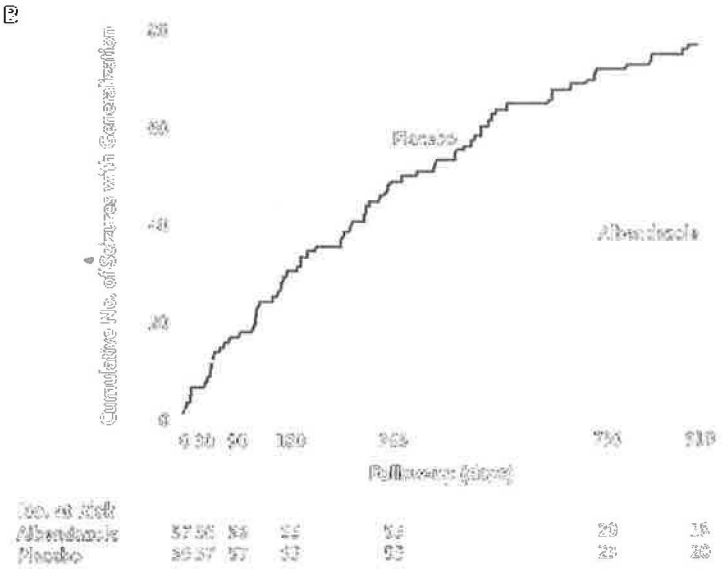
This was the first study evaluating the therapy of neurocysticercosis in a double-blinded fashion. It has been always hotly debated whether the use of albendazole or praziquantel would be effective in the therapy of neurocysticercosis. In this study in patients with active cysts, the addition of albendazole and steroids resulted in numbers of patients having significantly fewer seizures that generalized (Figure 4). Viable cysts disappeared more frequently in patients given medication as opposed to placebo. For the first time, a controlled study has demonstrated an actual long-term neurological benefit in these patients with therapy.

Figure 4: Cumulative Frequency and Seizures with Generalization



Garcia et al. NEJM. 2004
Jan;350:256

REFERENCES:

Bacterial Meningitis and Steroid Therapy

1. Ahmed A, Jafri H, Lutsar I, McCoig CC, et al. Pharmacodynamics of vancomycin for the treatment of experimental penicillin-and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother.* 1999;43:876-881.
2. Ahsan T, Shahid M, Mahmood T, Jabeen R, Jehangir U, Saleem M, Ahmed N, Shaheer A. Role of dexamethasone in acute bacterial meningitis in adults. *J Pak Med Assoc.* 2002 Jun;52(6):233-9.
3. Arditi M, Mason EO Jr, Bradley JS, et al. Three-year multicenter surveillance of pneumococcal meningitis in children: clinical characteristics and outcome related to penicillin susceptibility and dexamethasone use. *Pediatrics.* 1998;102(5):1087-97.
4. Armstrong RW, Fung PC. Brainstem encephalitis (Rhombencephalitis) due to *Listeria monocytogenes*: Case report and review. *Clin Infect Dis* 1994;16:689-702.
5. Arsene O, Linassier C, Quentin R, Legras A, Colombat P. Development of listeriosis during vancomycin therapy in a neutropenic patient. *Scand J Infect Dis.* 1996;28:415-6.
6. Baldassarre JS, Ingerman MJ, Nansteel J, Santoro J. Development of Listeria meningitis during vancomycin therapy: a case report. *J Infect Dis.* 1991;164(1):221-2.
7. Baltas I, Tsoulfa S, Sakellariou P, Vogas V, Fylaktakis M, Kondodimou A. Posttraumatic meningitis: bacteriology, hydrocephalus, and outcome. *Neurosurgery.* 1994;35(3):422-6.
8. Banerji C, Wheeler DC, Morgan JR. *Listeria monocytogenes* CAPD peritonitis: failure of vancomycin therapy. *J Antimicrob Chemother* 1994;33(2):374-5.
9. Bohr V, Rasmussen N, Hansen B, et al. Pneumococcal meningitis: an evaluation of prognostic factors in 164 cases based on mortality and on a study of lasting sequelae. *J Infect. 1985*;10(2):143-57.
10. de Gans J, van de beek D, for the European Dexamethasone in Adulthood Bacterial Meningitis Study investigators. Dexamethasone in adults with bacterial meningitis. *N Engl J Med.* 2002;347(20):1549-56.
11. Domingo P, Barquet N, Alvarez M, Coll P, Nava J, Garau J. Group B streptococcal meningitis in adults: report of twelve cases and review. *Clin Infect Dis.* 1997;25(5):1180-7.
12. Dryden MS, Jones NF, Phillips I. Vancomycin therapy failure in Listeria monocytogenes peritonitis in a patient on continuous ambulatory peritoneal dialysis. *J Infect Dis.* 1991 Dec;164(6):1239.
13. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS, Swartz MN. Acute bacterial meningitis in Adults – A Review of 493 Episodes. *N Engl J Med*, 1993 Jan;328(1):21-28.
14. Gorse GJ, Thrupp LD, Nudleman KL, et al. Bacterial meningitis in the elderly. *Arch Intern Med.* 1984;144(8):1603-7.

15. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Eng J Med.* 2001 Dec 13;345:1727-1733.
16. Kastenbauer S, Winkler F, Pfister HW, Bruzzi JF, Brennan DD, Tokuda Y, Nakazato N, Segal S, Tattevin P, Bruneel F, Régnier B, Hasbun R, Quagliarello V, Steigbigel NH. Cranial CT before lumbar puncture in suspected meningitis. *N Engl J Med.* 2002;346:1248-1251.
17. Jang TN, Wang FD, Wang LS, et al. Gram-negative bacillary meningitis in adults: a recent six-year experience. *J Formos Med Assoc.* 1993;92(6):540-546.
18. Joffe AR. Dexamethasone in adults with bacterial meningitis. *N Engl J Med.* 2003 Mar 6;348(10):954-7;author reply 954-7.
19. Kennedy WA, Hoyt MJ, McCracken GH Jr. The role of corticosteroid therapy in children with pneumococcal meningitis. *Am J Dis Child.* 1991;145(12):1374-1378.
20. Khetsuriani N, Quiroz ES, Holman RC, Anderson LJ. Viral meningitis-associated hospitalizations in the United States. *Neuroepidemiology*. 2003 Nov-Dec;22(6):345-52.
21. Lebel MH, Freij BJ, Syrogiannopoulos GA, et al. Dexamethosone therapy for bacterial meningitis: results of two double-blind, placebo-controlled tirals. *N Engl J Med.* 1988;319:964-71.
22. McIntyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. *JAMA.* 1997;278(11):925-931.
23. Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with Listeria monocytogenes. 33 years' experience at a general hospital and review of 776 episodes from the literature. Medicine (Baltimore). 1998 Sep;77(5):313-36.
24. Odio CM, Faingezicht I, Paris M, et al. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. *N Engl J Med* 1991;324:1525-31.
25. Prasad K, Volmink J, Menon GR. Steroids for treating tuberculous meningitis. *Cochrane Database Syst Rev.* 2000;(3):CD002244.
26. Reefhuis J, Honein M, Whitney CG, Chamany S, Mann EA, Biernath KR, Broder K, Manning S, Avashia S, Victor M, Costa P, Devine O, Graham A, Boyle C. Risk of Bacterial Meningitis in Children with Cochlear Implants. 2003 Jul 31;349(5):435-445
27. Richards SJ, Lambert CM, Scott AC. Recurrent Listeria monocytogenes meningitis treated with intraventricular vancomycin. *J Antimicrob Chemother.* 1992 Mar;29(3):351-3.
28. Schaad UB, Kaplan LS, McCracken GH Jr. Steroid therapy for bacterial meningitis. *Clin Infect Dis.* 1995;20(3):685-690.
29. Shafran SD. Dexamethasone improved disability in acute bacterial meningitis. *ACP Journal Club*, 2003 May-Jun;138:60.
30. Steigbigel NH. Computed tomography of the head before a lumbar puncture in suspected meningitis – is it helpful? *N Engl J Med.* 2001;345(24):1768-1770.

31. Tabas JA, Chambers HF, Tancredi DN, Binder WD, Abril V, Ortega E, Joffe AR, Poshkus M, Obaro S, de Gans J, van de Beek D, Tunkel AR, Scheld WM. Dexamethasone in adults with bacterial meningitis. N Engl J Med. 2003 Mar 6;348:10.
32. Thomas R, Le Tulzo Y, Bouget J, Camus C, Michelet C, Le Corre P, Bellissant E. Trial of dexamethasone treatment for severe bacterial meningitis in adults. Adult meningitis Steroid Group. *Intensive Care Med*. 1999 May;25(5):475-80.
33. Townsend GC, Scheld WM. The use f corticosteroids in the management of bacterial meningitis in adults. *J Antimicrob Chemother.* 1996;37(6):1051-1061.
34. Tokonami F, Imamura S, Suga M, Tokunaga K, Fukuda Y. A case of Listeria rhombencephalitis with a secondary vasculi suggested by MRI. *Rinsho Shinkeigaku.* 1993 Jun;33(6):637-41.
35. van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids in acute bacterial meningitis. *Cochrane Database Syst Rev*. 2003;(3):CD004305.

Drug-Induced Aseptic Meningitis

36. Blumenfeld H, Cha JH, Cudkowicz ME. Trimethoprim and sulfonamide-associated meningoencephalitis with MRI correlates. *Neurology*. 1996 Feb;46(2):556-8.
37. Eustace S, Buff B. Magnetic resonance imaging in drug-induced meningitis. *Can Assoc Radiol J.* 1994 Dec;45(6):463-5.
38. Food and Drug Administration, Rockville, MD 20852. Aseptic meningitis and intravenous immunoglobulin therapy. *Ann Intern Med.* 1994 August 15;121(4):305-306.
39. Gordon MF, Allon M, Coyle PK. Drug-induced meningitis. *Neurology*. 1990 Jan;40(1):163-4.
40. Jolles S, Sewell WA, Leighton C. Drug-induced aseptic meningitis: diagnosis and management. *Drug Saf*. 2000 Mar;22(3):215-26.
41. Kato T, Suzuki E, Sone M, Yoshida E, Hirayama M. A case of recurrent aseptic meningitis caused by high-dose intravenous gammaglobulin therapy for chronic inflammatory demyelinating polyneuropathy. *Rinsho Shinkeigaku*. 2001 Nov;41(11):797-800.
42. Sekul EA, Cupler EJ, Dalakas MC. Aseptic Meningitis Associated with High-Dose Intravenous Immunoglobulin Therapy. *Ann Intern Med.* 1994 August 15;121(4):259-262.
43. Mathy I, Gille M, Van Raemdonck F, Delbecq J, Depre A. Neurological complications of intravenous immunoglobulin (IVIg) therapy: an illustrative case of acute encephalopathy following IVIg therapy and a review of the literature. *Acta Neurol Belg*. 1998 Dec;98(4):347-51.
44. Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. *Arch Intern Med.* 1999 Jun 14;159(11):1185-94.
45. Muller MP, Richardson DC, Walmsley, SL. Trimethoprim-sulfamethoxazole induced aseptic meningitis in a renal transplant patient. *Clin Nephrol*. 2001 Jan;55(1):80-4.

46. Patey O, Lacheheb A, Dellion S, Zanditenas D, Jungfer-Bouvier F, Lafai C. A rare case of cortrimoxazole-induced eosinophilic aseptic meningitis in an HIV-infected patient. *Scand J Infect Dis.* 1998;30(5):530-1.

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47. Abbas BB, Abdolvahab A, Gholamali YP, Roshanak B, Mahmood R. Clinical signs as a guide for performing HSV-PCR in correct diagnosis of herpes simplex virus encephalitis. *Neurol India.* 2003 Sep; 51(3):341-4.
48. Archard JM, Duverlie G, Schmit JL, Lebon P, Veyssier P, Fournier A. Mollaret's meningitis and herpes simplex virus type 1 [letter]. *N Engl J Med.* 1992;326:893-894.
49. Aurelius E, Johansson B, Sköldenberg B, Forsgren M. Encephalitis in immunocompetent patients due to herpes simplex virus type 1 or 2 as determined by type-specific polymerase chain reaction and antibody assays of cerebrospinal fluid. *J Med Virol.* 1993;39:179-186
50. Barnett EM, Jacobsen G, Evans G, et al. Herpes simplex encephalitis in the temporal cortex and limbic system after trigeminal nerve inoculation. *J Infect Dis.* 1994;169:782-6.
51. Chu K, Kang DW, Lee JJ, Yoon BW. Atypical brainstem encephalitis caused by herpes simplex virus 2. *Arch Neurol.* 2002 Mar;59:460-463.
52. Ciardi M, Giacchetti G, Fedele CG, Tenorio A, Brandi A, Libertone R, Ajassa C, Borgese L, Delia S. Acute Cerebellitis caused by herpes simplex virus type 1. *Clin. Inf. Dis.* 2003;36:e50-e54.
53. de Tiège X, Héron B, Lebon P, Ponsot G, Rozenberg F. Limits of early diagnosis of herpes simplex encephalitis in children: a retrospective study of 38 cases. *Clinical Infectious Diseases.* 2003;36:1335-1339.
54. Dennett C, Klapper PE, Cleator GM. Polymerase chain reaction in the investigation of "relapse" following herpes simplex encephalitis. *J Med Virol.* 1996;48:129-132.
55. Fodor PA, Levin MJ, Weinberg A, Sandberg E, Sylman J, Tyler KL. Atypical herpes simplex virus encephalitis diagnosed by PCR amplification of viral DNA from CSF. *Neurology.* 1998 Aug;51(2):554-9.
56. Garcia de Tena J, de Pablo Sanchez R, Daguerre Talou M, Lopez Matamala B, Martinez Diaz C. The value of the polymerase chain reaction in cerebrospinal fluid for the diagnosis of herpetic encephalitis: a report of 2 cases and a review of the literature. *An Med Interna.* 2000 Feb;17(2):81-3.
57. Graman PS. Mollaret's meningitis associated with acute Epstein-Barr virus mononucleosis. *Arch Neurol.* 1987;44(11):1204-1205.
58. Harrison NA, MacDonald BK, Scott G, Kapoor R. Atypical herpes type 2 encephalitis associated with normal MRI imaging. *J Neurology Neurosurgery Psychiatry.* 2003;74:974-976.
59. Jenseuius M, Myrvang B, Storvold G. Mollaret meningitis. Is the riddle finally solved? Tidsskr Nor Laegeforen. 1997 June 20;117(16):2319-21.

60. Jensenius M, Myrvang B, Storvold G, Bucher A, Hellum KB, Bruu AL. Herpes simplex virus type 2 DNA detected in cerebrospinal fluid of 9 patients with Mollaret's meningitis. *Acta Neurol Scand.* 1998;98:209-212.
61. Kojima Y, Hashiguchi H, Hashimoto T, Tsuji S, Shoji H, Kazuyama Y. Recurrent herpes simplex virus type 2 meningitis: a case report of Mollaret's meningitis. *Jpn. J. Infect. Dis.*:2002;55:85-88.
62. Koskiniemi M, Piiparinen H, Mannonen L, Rantalaiho T, Vaheri A. Herpes encephalitis is a disease of middle aged and elderly people: polymerase chain reaction for detection of herpes simplex virus in the CSF of 516 patients with encephalitis. The study group. *J Neurol Neurosurg Psychiatry.* 1996;60(2):174-178.
63. Mitchell PS, Espy MJ, Smith TF, Toal DR, Rys PN, Berbari EF, Osmon DR, Persing DH. Laboratory diagnosis of central nervous system infections with herpes simplex virus by PCR performed with cerebrospinal fluid specimens. *J Clin Microbiol.* 1997 Nov;35(11):2873-2877.
64. Mollaret P. La méningite endothélio-leucocytaire multirécurrente bénigne: syndrome nouveau ou maladie nouvelle? *Rev Neurol.* 1944;76:57-76.
65. To the Editor: Mollaret's meningitis and herpes simplex virus type 1. *N Engl J Med.* 1992 Mar;326(13):893-4.
66. Monteyne P, Albert F, Weissbrich B, Zardini E, Ciardi M, Cleator GM, Sindic CJM, The European Union Concerted Action on virus Meningitis and Encephalitis. The detection of intrathecal synthesis of anti-herpes simplex IgG antibodies: comparison between an antigen-medicated immunoblotting technique and antibody index calculations. Journal of Medical Virology. 53(4):324-331.
67. O'Sullivan CE, Aksamit AJ, Harrington JR, Harmsen WS, Mitchell PS; Patel R. Clinical spectrum and laboratory characteristics associated with detection of herpes simplex virus DNA in cerebrospinal fluid. *Mayo Clin Proc.* 2003;78:1347-1352.
68. Puchhammer-Stockl E, Presterl E, Croy C, Alberle S, Popow-Kraupp T, Kundi M, Hofmann H, Wenninger U, Godl I. Screening for possible failure of herpes simplex virus PCR in cerebrospinal fluid for the diagnosis of herpes simplex encephalitis. *J Med Virol.* 2001 Aug;64(4):531-6.
69. Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, Lebon P, Canton P, Rozenberg F, for the French Herpes Simplex Encephalitis Study Group. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. *Clinical Inf Dis* 2002;35:254-260.
70. Sauerbrei A, Wutzler P. Laboratory diagnosis of central nervous system infections caused by herpesviruses. *J Clin Virology.* 2002 July:25;45-51.
71. Shafran SD. Herpes simplex encephalitis. *N Engl J Med.* 1996;335(3):209.
72. Sindic CJM, Van Antwerpen MP, Goffette S. Clinical relevance of polymerase chain reaction (PCR) assays and antigen-driven immunoblots for the diagnosis of neurological infectious diseases. *Brain Research Bulletin.* 2003 Aug;61(3):299-308.
73. Tebas P, Nease RF, Storch GA. Use of the polymerase chain reaction in the diagnosis of herpes simplex encephalitis: a decision analysis model. *Am J Med.* 1998;105(4):287-295.

74. Tedder DG, Ashley R, Tyler KL, Levin MJ. Herpes simplex virus infection as a cause of benign recurrent lymphocytic meningitis. *Ann Intern Med.* 1994;121:334-338.
75. Weil AA, Glaser CA, Amad Z, Forghani B. Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result. *Clin. Inf. Dis.* 2002;34:1154-1157.
76. Whitley RJ, Lakeman F. Herpes simplex virus infections of the central nervous system: therapeutic and diagnostic considerations. *Clin Infect Dis.* 1995;20:414-20.

The Etiologies of Encephalitis, VZV Encephalitis

77. Brown M, Scarborough M, Brink N, Manji H, Miller R. Varicella zoster virus-associated neurological disease in HIV-infected patients. *Int J STD AIDS.* 2001 Feb;12(2):79-83.
78. Calvario A, Bozzi A, Scarasciulli M, Ventola C, Seccia R, Stomati D, Brancasi B. Herpes Consensus PCR test: a useful diagnostic approach to the screening of viral diseases of the central nervous system. *J Clin Virol.* 2002 Jul;25 Suppl 1:S71-8.
79. Caminero AB, Pareja JA, Echevarria JM, de Ory F. Myellitis associated with varicella-zoster virus in the absence of cutaneous zoster. *Rev Neurol.* 1996;24(136):1532-5.
80. Carol A. Glaser, Sabrina Gilliam, David Schnurr, Bagher Forghani, Somayeh Honarmand, Nino Khetsuriani, Marc Fischer, Cynthia K. Cossen, and Larry J. Anderson. In Search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project,1998-2000. *Clinical Infectious Diseases* 2003;36:731-742.
81. Corral I, Quereda C, Antela A, Pintado V, Casado JL, Martin-Davila P, Navas E, Moreno S. Neurological complications of varicella-zoster virus in human immunodeficiency virus-infected patients: changes in prevalences and diagnostic utility of polymerase chain reaction in cerebrospinal fluid. *J Neurovirol.* 2003 Feb;9(1):129-35.
82. De La Blanchardiere A, Rozenberg F, Caumes E, Picard O, Lionnet F, Livartowski J, Coste J, Sicard D, Lebon P, Salmon-Ceron D. Neurological complications of varicella-zoster virus infection in adults with human immunodeficiency virus infection. *Scand J Infect Dis.* 2000;32(3):263-9.
83. Fujimoto S, Kobayashi M, Uemura O, Iwasa M, Ando T, Katoh T, Nakamura C, Maki N, Togari H, Wada Y. PCR on cerebrospinal fluid to show influenza-associated acute encephalopathy or encephalitis. *Lancet.* 1998 Sep 12;352(9131):873-5.
84. Gilden DH, Bennett JL, Kleinschmidt-DeMasters BK, Song DD, Yee AS, Steiner I. The value of cerebrospinal fluid antiviral antibody in the diagnosis of neurologic disease produced by varicella zoster virus. *J Neurol Sci.* 1998;159(2):140-144.
85. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med.* 2000 March 2;342(9):635-645.

86. Ginsberg L, Compston DAS. Acute encephalopathy: diagnosis and outcome in patients at a regional neurological unit. *Quarterly Journal of Medicine*. 1994;87:169-180.
87. Gnann JW Jr. Varicella-zoster virus: atypical presentations and unusual complications. *The Journal of Infectious Diseases*. 2002;186:S91-S98.
88. Hirai T, Korogi Y, Hamatake S, et al. Case report: varicella-zoster virus myelitis--serial MR findings. *Br J Radiol.* 1996;69(828):1187-90.
89. Kenyon LC, Dulaney E, Montone KT, et al. Varicella-zoster ventriculo-encephalitis and spinal cord infarction in a patient with AIDS. *Acta Neuropathol (Berl).* 1996;92(2):202-5.
90. Koskiniemi M, Rantalaiho T, Piiparinen H, von Bonsdorff CH, Farkkila M, Jarvinen A, Kinnunen E, Koskiniemi S, Mannonen L, Muttilainen M, Linnavuori K, Porras J, Puolakkainen M, Raiha K, Salonen EM, Ukkonen P, Vaheri A, Valtonen V; Study Group. Infections of the central nervous system of suspected viral origin a collaborative study from Finland. *J Neurovirol.* 2001 Oct;7(5):400-8.
91. Luby JP, Infections of the central nervous system. *Am J med Sci.* 1992;304(6):379-391.
92. Majid A, Galetta SL, Sweeney CJ, Robinson C, Mahalingam R, Smith J, Forghani B, Gilden DH. Epstein-Barr virus myeloradiculitis and encephalomyeloradiculitis. *Brain.* 2002 Jan 1;125(1):159-165.
93. Markoulatos P, Georgopoulou A, Siafakas N, Plakokefalos E, Tzanakak G, Kourea-Kremastinou J. Laboratory diagnosis of common herpesvirus infections of the central nervous system by a multiplex PCR assay. *J Clin Microbiol.* 2001 Dec;39(12):4426-32.
94. McCullers JA, Facchini S, Chesney PJ, Webster RG. Infuenza B virus encephalitis. *Clin Infect Dis.* 1999 Apr;28(4):898-900.
95. McCullers JA, Lakeman FD, Whitley RJ. Human herpesvirus 6 is associated with focal encephalitis. *Clin Infect Dis.* 1995 Sep;21(3):571-6.
96. McKelvie PA, Collins S, Thyagarajan D, Trost N, Sheorey H, Byrne E. Meningoencephalomyelitis with vasculitis due to varicella zoster virus: a case report and review of the literature. *Pathology.* 2002 Feb;34(1):88-93.
97. Morch K, Fylkesnes SI, Haukenes G. Meningitis associated with reactivation of varicella-zoster virus. *Tidsskr Nor Laegeforen.* 2003 Oct 23;123(20):2871-3.
98. Nowak DA, Boehmer R, Fuchs H-H. A retrospective clinical, laboratory and outcome analysis in 43 cases of acute aseptic meningitis. *European Journal of Neurology.* 2003 May;10(3):271.
99. Pina MA, Ara JR, Capablo JL, Omenaca M. Myelitis and optic neuritis caused by varicella. *Rev Neurol.* 1997;25(146):1575-6.
100. Schaller B, Bernhard P, Graber P, Steck AJ. Cerebellar syndrome after varicella infection without virus identification in cerebrospinal fluid—an important differential ataxia diagnosis. *Schweiz Rundsch Med Prax.* 1999 Nov 11;88(46):1901-7.
101. Sindic CJM, Van Antwerpen MP, Goffette S. Clinical relevance of polymerase chain reaction (PCR) assays and antigen-driven immunoblots for the diagnosis of neurological infectious diseases. *Brain Research Bulletin.* 2003 Aug 15;61(3):299-308.

102. Solomon T. Exotic and emerging viral encephalitides. *Curr Opin Neurol.* 2003 Jun;16(3):411-8.
103. Studahl M, Bergstrom T, Hagberg L. Acute viral encephalitis in adults—a prospective study. *Scand J Infect Dis.* 1998;30(3):215-20.
104. Tauro S, Toh V, Osman H, Mahendra P. Varicella zoster meningoencephalitis following treatment for dermatomal zoster in an alloBMT patient. *Bone Marrow Transplantation.* 2000 Oct;26(7):795-796.

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105. Alpert SG, Fergerson J, Noël LP. Intrauterine West Nile virus: ocular and systemic findings. *American Journal of Ophthalmology.* 2003 Oct; 136(4):733-735.
106. Anninger WV, Lomeo MD, Dingle J, Epstein AD, Lubow M. West nile virus-associated optic neuritis and chorioretinitis. *American Journal of Ophthalmology.* 2003 Dec;136(6):1183-1185.
107. Bosanko CM, Gilroy J, Wang AM, Sanders W, Dulai M, Wilson J, Blum K. West Nile Virus Encephalitis involving the Substantia Nigra. *Archives of Neurology.* 2003 Oct;60(10):1448-1452.
108. Butman J. MR Imaging Helps Confirm West Nile Virus Encephalitis. *Radiological Society of North America.* 2003 Feb.
109. Cerna, F, Mehrad B, Luby JP, Burns D, Fleckenstein JL. St. Louis encephalitis and the substantia nigra: MR imaging evaluation. *Am J Neuroradiol.* 1999 Aug;20:1281-1283.
110. Chandler LJ, Nordoff NG. Identification of genetic variation among St. Louis encephalitis virus isolates, using single-strand conformation polymorphism analysis. *J Virol Methods.* 1999 Jul;80(2):169-78.
111. Chowers MY, Lang R, Nassar F, Ben-David D, Giladi M, Rubinshtein E, Itzhaki A, Mishal J, Siegman-Igra Y, Kitzes R, Pick N, Landau Z, Wolf D, Bin H, Mendelson E, Pitlik SD, Weinberger M. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. *Emerging Infectious Diseases.* 2001 Jul-Aug;7(4).
112. DeSalvo D, Roy-Chaudhury P, Peddi R, Merchen T, Konijetti K, Gupta M, Boardman R, Rogers C, Buell J, Hanaway M, Broderick J, Smith R, Woodle ES. West Nile virus encephalitis in organ transplant recipients: another high-risk group for meningoencephalitis and death. *Transplantation.* 2004 Feb 15;77(3):466-469.
113. Einsiedel L, Kat E, Ravindran J, Slavotinek J, Gordon DL. MR findings in Murray Valley encephalitis. *American Journal of Neuroradiology.* 2003 Aug;24:1379-1382.
114. Hadler J, Nelson R, McCarthy T, Andreadis T, Lis MJ, French R, Beckwith W, Mayo D, Archambault G, Cartter M. *Emerging Infectious Diseases.* 2001 Jul-Aug;7(4):636-42.
115. Haley M, Retter AS, Fowler D, Gea-Banacloche J, O'Grady NP. The Role for intravenous immunoglobulin in the treatment of West Nile Virus encephalitis. *Clinical Infectious Diseases.* 2003;37:e88-e90.

116. Hershberger VS, Augsburger JJ, Hutchins RK, Miller SA, Horwitz JA, Bergmann M. Chorioretinal lesions in nonfatal cases of West Nile virus infection. *Ophthalmology*. 2003 Sep;110(9):1732-6.
117. Komar N, Langevin S, Hinten S, Nemeth N, Edwards E, Hettler D, Davis B, Bowen R, Bunning M. Experimental Infection of North American Birds with the New York 1999 Strain of West Nile Virus. *Emerging Infectious Diseases*. 2003 March;9(3).
118. Kumar D, Prasad GVR, Zaltzman J, Levy GA, Humar A. Community-acquired West Nile virus infection in solid-organ transplant recipients. *Transplantation.* 2004 Feb 15;77(3):399-402.
119. Omalu BI, Shakir AA, Wang G, Lipkin WI, Wiley CA. Fatal fulminant pan-meningo-polioencephalitis due to West Nile virus. *Brain Pathology.* 2003 Oct;13(4):465-72.
120. Panella NA, Kerst AJ, Lanciotti RS, Bryant P, Wolf B. Komar N. Comparative West Nile Virus detection in organs of naturally infected American crows (Corvus brachyrhynchos). *Emerging Infectious Diseases*. 2001 Jul-Aug;7(4).
121. Pealer LN, Marfin AA, Petersen LR, Lanciotti RS, Page PL, Stramer SL, Stobierski MG, Signs K, Newman B, Kapoor H, Goodman JL, Chamberland ME, for the West Nile Virus transmission investigation team. transmission of West Nile Virus through blood transfusion in the United States in 2002. *The New England Journal of Medicine.* 2003 Sept 25;349(13):1236-1245.
122. Shi PY, Wong SJ. Serologic diagnosis of West Nile virus infection. *Expert Rev Mol Diagn.* 2003 Nov;3(6):733-41.
123. Xiao SY, Guzman H, Zhang H, Travassos da Rosa A, Tesh RB. West Nile Virus Infection in the Golden Hamster *(Mesocricetus auratus)*: A Model for West Nile Encephalitis. *Emerging Infectious Diseases*. 2001 Jul-Aug;7(4).

Neurocysticercosis

124. Garcia HH, Pretell EJ, Gilman RH, Martinez SM, Moulton LH, Del Brutto OH, Herrera G, Evans CAW, Gonzalez AE, for the Cysticercosis Working Group in Peru. *NEJM*. 2004 Jan;350:249-258.