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mozygosity may therefore represent a new approach in the genetic counseling of persons who carry the gene for retinoblastoma.

The unexpectedly high frequency of chromosome 13 homozygosity in retinoblastomas has implications for the search for the chromosomal loci of other possible recessive alleles important in the genesis of other tumors. Assuming the same incidence of chromosome homozygosity in the genesis of these tumors, one could perform these studies with a small set of constitutional and tumor cells, given a battery of DNA or enzyme polymorphisms that span the genome.

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VENTRICULOSTOMY-RELATED INFECTIONS

A Prospective Epidemiologic Study

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Abstract We conducted a prospective epidemiologic study of ventriculostomy-related infections (ventriculitis or meningitis) in 172 consecutive neurosurgical patients over a two-year period to determine the incidence, risk factors, and clinical characteristics of the infections. Ventriculitis or meningitis developed in 19 of 172 patients (11 per cent) undergoing a total of 213 ventriculostomies. When data from all these cases plus five cases of nonventriculostomy-related infection were combined, cerebrospinal-fluid pleocytosis was more significantly associated with the diagnosis of ventriculitis or meningitis ($P < 0.0001$) than were fever and leukocytosis ($P = 0.07$). Risk factors for ventriculostomy-related infec-

tions included intracerebral hemorrhage with intraventricular hemorrhage ($P = 0.027$), neurosurgical operations ($P = 0.016$), intracranial pressure of 20 mm Hg or more ($P = 0.019$), ventricular catheterization for more than five days ($P = 0.017$), and irrigation of the system ($P = 0.021$). Previous ventriculostomy did not increase the risk of infection with subsequent procedures. We conclude that ventriculostomy-related infections may be prevented by maintenance of a closed drainage system and by early removal of the ventricular catheter. If monitoring is required for more than five days, the catheter should be removed and inserted at a different site. (*N Engl J Med* 1984; 310:553-9.)

RECENT years have witnessed a dramatic increase in the use of techniques for monitoring intracranial pressure in a variety of neurologic disorders, especially trauma.¹⁻⁶ Intraventricular catheterization (ventriculostomy) is considered to be the procedure of choice, but enthusiasm for the considerable diagnostic, prognostic, and therapeutic value of this technique

has always been somewhat dampened by the potential risks of infection and hemorrhage.¹ In the spring of 1979 six patients in the Neurosurgery Intensive Care Unit at the Medical College of Virginia contracted ventriculitis or meningitis after undergoing ventriculostomy. When a retrospective epidemiologic investigation failed to reveal a source of infection, a mode of transmission, or risk factors for infection, a prospective epidemiologic investigation was initiated. The objectives of the study were to determine the incidence of ventriculostomy-related infections, to analyze the relation between positive cultures of cerebrospinal fluid and the clinical and laboratory findings usually associ-

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ated with ventriculitis and meningitis, and to identify the risk factors for occurrence of ventriculostomy-related infection.

METHODS

Patients

All patients admitted to the Neurosurgery Service who had undergone a ventriculostomy between April 1979 and June 1981 were studied. Ventricular catheters were used to monitor patients with head trauma, intraventricular hemorrhage, brain tumor, or subarachnoid hemorrhage. The duration of monitoring was determined by the level of intracranial pressure and the clinical condition of the patient.

Technique for Insertion of Ventricular Catheters

After the patient's head had been completely shaved, the scalp was prepped with povidone-iodine solution and draped. A small incision was made over the coronal suture in line with the pupil of the eye. A twist drill hole was then made through the skull, and the dura was lacerated with the drill. A No. 5 pediatric feeding tube was introduced after it had been tunneled from a site on the scalp approximately 4 to 6 cm from the initial incision. After the ventricular catheter had been inserted into the appropriate lateral ventricle, the wound was closed with suture, and the catheter was sewn to the scalp to prevent dislodgement. Some patients were given prophylactic nafcillin (1 g) intravenously every six hours for a total of four doses starting at the time when the ventricular catheter was inserted.

Clinical and Epidemiologic Data

Information collected when patients entered the study included age, sex, race, date of admission to the hospital, diagnosis (or diagnoses) on admission, and underlying diseases. A record was kept of all surgical operations and all types of instrumentation. Clinical observations recorded included temperature, signs of wound infection, and presence of cerebrospinal-fluid leaks. A record was kept of peripheral white-cell counts and of all radiologic studies. The results of cultures of blood, urine, sputum, and purulent exudate from wounds and of antimicrobial-susceptibility tests for each isolate were noted.

Observations of Ventriculostomy Systems

The place in the hospital where the ventriculostomy was performed (operating room or intensive-care unit) was noted. Cerebrospinal fluid for culture was aspirated from the ventricular catheter or drainage system at the time of insertion. Whether or not cerebrospinal fluid drained through the ventriculostomy system and the highest intracranial pressure were recorded. A record of problems and manipulations of the ventriculostomy system (Fig. 1) was maintained at each patient's bedside by nurse epidemiologists conducting the prospective study and by nurses in the intensive-care unit. The record included leaks in the system, accidental disconnections, and replacement of syringes on the manifold. Recorded manipulations included changes in the cerebrospinal-fluid bag, changes in the pressure tubing, irrigation of the system with a syringe, and dressing changes at the ventriculostomy site. The appearance of gross blood in the ventriculostomy system was noted. Also re-

corded were the results of all cultures of cerebrospinal fluid obtained either by aspiration from the ventricular catheter or by lumbar puncture while the catheter was in place or within two weeks after its removal and the results of antimicrobial-susceptibility tests. Cerebrospinal fluid obtained from the ventricular catheter or by lumbar puncture was analyzed for cell counts.

Samples of cerebrospinal fluid for culture were aspirated from the ventricular catheter just before its removal. Patients were followed for two weeks after the catheter had been removed. During this period, patients were observed for signs of meningitis and for clinical outcome.

Microbiology

Samples of cerebrospinal fluid obtained by lumbar puncture, as well as samples of blood, urine, sputum, and exudate from wounds, were cultured in the hospital laboratory. All other specimens for culture were processed in the Epidemiology Unit laboratory. Cerebrospinal fluid aspirated from the ventricular tubing was cultured quantitatively if the volume obtained was adequate. If only a few drops could be obtained, the fluid was inoculated onto a blood-agar plate and into brain-heart infusion broth. In both laboratories gram-positive cocci were identified by standard techniques. Gram-negative bacilli were identified with the API20E system (Analytab Products, Plainview, N.Y.). All isolates were tested for susceptibility to antibiotics in the hospital laboratory by an agar-dilution technique.⁷

Definitions

The definition of ventriculostomy-related infection was developed before the study began. Definitions of fever, leukocytosis, and pleocytosis were developed after the study had been initiated, when we decided to study the relation of these variables to ventriculitis or meningitis as diagnosed by positive cultures of cerebrospinal fluid.

For a diagnosis of ventriculitis or meningitis related to ventriculostomy, the following criteria had to be met: (1) no other detectable

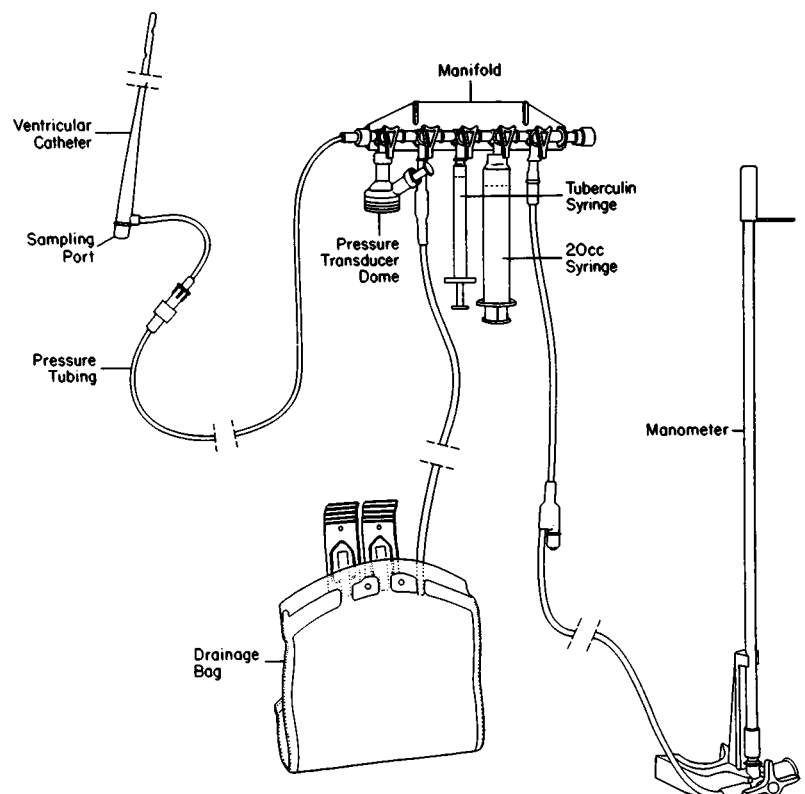


Figure 1. Ventricular Catheter and System Used for Monitoring Intracranial Pressure and Draining Cerebrospinal Fluid.

source of central-nervous-system infection, such as cerebrospinal-fluid leaks, concurrent bacteremia with the same organism as that isolated from cerebrospinal fluid, or penetrating injury of the central nervous system; (2) negative cultures of cerebrospinal fluid obtained at the time of ventriculostomy; (3) ventricular catheterization for 24 hours or longer; and (4) documentation of ventricular or meningeal infection by positive cultures of cerebrospinal fluid obtained by aspiration from the ventricular catheter or by lumbar puncture.

Fever was defined as a temperature of 38°C or higher. For fever to be attributed to ventriculitis or meningitis the following criteria had to be met: (1) onset of fever within 48 hours before or after a cerebrospinal-fluid culture was found to be positive; (2) no evidence of infection at other body sites; (3) if the patient had fever 48 or more hours before the positive culture, a temperature rise of at least 0.6°C within 48 hours before or after the positive culture; and (4) fever persisting for at least three consecutive days.

Peripheral leukocytosis was defined as a white-cell count of at least 11,000 cells per cubic millimeter of blood. For peripheral leukocytosis to be attributed to ventriculitis or meningitis the following criteria had to be met: (1) onset of leukocytosis within 48 hours before or after the cerebrospinal-fluid culture was found to be positive; (2) no evidence of infection at other body sites; (3) if the white-cell count was at least 11,000 48 or more hours before the positive culture, an increase in the white-cell count of at least 1000 cells within 48 hours before or after the positive culture; and (4) leukocytosis persisting for at least three consecutive days.

Cerebrospinal-fluid pleocytosis was defined as a cerebrospinal-fluid white-cell count of at least 11 cells per cubic millimeter. For cerebrospinal-fluid pleocytosis to be attributed to ventriculitis or meningitis, the following criteria had to be met: (1) 50 per cent or more polymorphonuclear leukocytes in the white-cell count; (2) pleocytosis occurring within 48 hours before or after the cerebrospinal-fluid culture was found to be positive; (3) if pleocytosis was present 48 or more hours before the positive culture, an increase of at least 50 white cells per cubic millimeter within 48 hours before or after the positive culture; and (4) pleocytosis persisting for at least three consecutive days.

In patients without ventriculitis or meningitis, fever was defined as a temperature of 38°C or higher for three consecutive days, and leukocytosis was defined as a white-cell count of at least 11,000 cells per cubic millimeter for three consecutive days while the ventricular catheter was in place, without evidence of infection at other body sites. Pleocytosis was defined as a cerebrospinal-fluid white-cell count of at least 11 cells per cubic millimeter with 50 per cent or more polymorphonuclear leukocytes for three consecutive days while the catheter was in place.

Analysis of Data

Data were entered onto computer cards. In patients with multiple ventriculostomies, each catheterization was coded separately. Data were analyzed using the Statistical Analysis System and university computer resources. Tests of statistical significance included the chi-square test and Fisher's exact test. Analysis of interrelated variables was performed by the Statistical Analysis System Logistic Regression Procedure. A life-table analysis was performed using the BMDP1L procedure of the Biomedical Programs. Time-to-infection curves (survival curves) were compared using the generalized Wilcoxon (Breslow) test.

RESULTS

The study population comprised 172 patients undergoing 213 ventriculostomies. Nineteen patients (11 per cent) had a ventriculostomy-related infection, and 19 of the ventriculostomies (8.9 per cent) were complicated by infection. Patients with infection (13 male and 6 female) had a mean age of 39 years, with a range of 3 to 75; 10 were white and 9 were black. Patients without infection (109 male and 41 female) had a

mean age of 40 years, with a range of 1 to 89; 80 were white, 69 were black, and 1 was Asian. Patients with nonventriculostomy-related ventriculitis (two male and one female) had a mean age of 41 years, with a range of 23 to 64; all three were white.

Microbiology

The microorganisms that caused infection are listed in Table 1. Eleven ventriculostomy-related infections were diagnosed on the basis of a positive culture of cerebrospinal-fluid specimens obtained only from the ventricular catheter. In four specimens that were sufficient for quantitative culture, the concentrations of microorganisms ranged from 8×10^2 to 3×10^6 colony-forming units per milliliter. Cerebrospinal fluid from the ventricular catheters in the other seven patients was streaked on agar plates for culture. For three of the seven patients the growth on agar plates was reported as "too numerous to count." Of the other four, one had positive cultures from three consecutive specimens of cerebrospinal fluid collected over 48 hours, one had the same organism isolated from both ventricular cerebrospinal fluid and cerebrospinal fluid obtained at autopsy, and two had single cultures of ventricular cerebrospinal fluid reported as positive by growth on an agar plate. The latter two cultures were positive for *Staphylococcus aureus* and *Klebsiella pneumoniae*. Three ventriculostomy-related infections were diagnosed on the basis of a positive culture of cerebrospinal fluid obtained by lumbar puncture. Five patients had infection diagnosed on the basis of positive cultures of cerebrospinal fluid obtained both by aspiration from the ventricular catheter and by lumbar puncture. In each case, the same species with identical antibiotic sensitivity was recovered from both ventricular and lumbar cerebrospinal-fluid specimens.

Relation of Fever, Peripheral Leukocytosis, and Cerebrospinal-Fluid Pleocytosis to Ventriculitis or Meningitis

For analysis of the correlation between the presence of ventriculitis or meningitis and the occurrence of fever, peripheral leukocytosis, and cerebrospinal-fluid pleocytosis, data were combined from the 19 patients with ventriculostomy-related infection and the 5 with nonventriculostomy-related infection (Table 2). For 13 of 24 ventriculostomies (54 per cent) complicated by ventriculitis or meningitis and for 62 of 189 (33 per cent) not complicated by infection, there were infections at other body sites during catheterization. All these cases were excluded from the analysis, leaving only eight patients with ventriculitis or meningitis. The relations of fever and peripheral leukocytosis to ventriculitis or meningitis were only of borderline significance ($P = 0.07$). The predictive value of fever for ventriculitis or meningitis was only 0.113, and the predictive value of leukocytosis was only 0.095.

Cerebrospinal-fluid white-cell counts were performed for only 70 patients, but the relation between ventriculitis or meningitis and pleocytosis was significant ($P = 0.0001$). Four patients with ventriculitis or

Table 1. Bacteria Isolated from the Cerebrospinal Fluid of 19 Patients with Ventriculostomy-Related Infection.

ISOLATES	NO. OF PATIENTS (%)
Gram-positive	9 (47)
Coagulase-negative staphylococci	6 (32)
<i>Staphylococcus aureus</i>	1 (5)
<i>Streptococcus faecalis</i>	1 (5)
<i>Str. mitis</i>	1 (5)
Gram-negative	10 (53)
<i>Enterobacter aerogenes</i>	2 (11)
<i>Ent. cloacae</i>	2 (11)
<i>Acinetobacter calcoaceticus</i>	2 (11)
<i>Escherichia coli</i>	1 (5)
<i>Klebsiella pneumoniae</i>	1 (5)
<i>Serratia marcescens</i>	1 (5)
<i>Providencia stuartii</i>	1 (5)

meningitis had a white-cell count above 11 cells per cubic millimeter during the period 48 or more hours before the positive culture; one count rose by 229 cells and the other three by over 500 cells. In spite of the high level of significance, four patients with ventriculitis or meningitis did not have elevated cerebrospinal-fluid white-cell counts. Two of these patients had ventriculitis or meningitis due to coagulase-negative staphylococci, one had infection due to *Staph. aureus*, and one had infection due to *Enterobacter cloacae*. The predictive value of cerebrospinal-fluid pleocytosis was 0.538.

Risk Factors for Ventriculostomy-Related Infection

Many potential risk factors for ventriculostomy-related infection were examined. The results of this analysis are shown in Table 3.

The duration of ventricular catheterization was significantly related to the occurrence of infection, with a significantly higher infection rate when the catheter had been in place for more than five days. A life-table analysis revealed that the risk of infection was 9 per cent at Day 5 but was 21, 37, and 42 per cent by Days 8, 10, and 11, respectively. Since patients with intraventricular hemorrhage and an intracranial pressure of 20 mm Hg or higher may need intracranial-pressure monitoring and cerebrospinal-fluid drainage for longer periods, these variables were further tested for their relation to ventriculostomy-related infection by a stepwise logistic-regression analysis. If the ventriculostomy catheter was in place for more than five days ($P = 0.034$), both intracerebral hemorrhage with intraventricular hemorrhage ($P = 0.01$) and an intracranial pressure of 20 mm Hg or

more ($P = 0.01$) remained risk factors for ventriculostomy-related infections.

Although five potential risk factors were found to be significantly associated with ventriculostomy-related infection, some significant associations may have been missed because of the low statistical power that resulted from analysis of a small number of infections in comparison to the large number of ventriculostomies that were not complicated by infection.

No patient who had a ventriculostomy-related infection and was not treated survived, but some of these patients probably died of underlying neurosurgical disease or injury. There was a significant association between ventriculostomy-related infection and mortality. When time-to-infection (survival) curves were compared for patients who survived and those who did not, patients who died had a higher risk of infection ($P = 0.029$).

DISCUSSION

The 8.9 per cent incidence of ventriculostomy-related infection in our series falls within the previously reported range of 0 to 27 per cent.⁸⁻¹⁴ Differences between our rate and those in other studies may be real or may be due to differences in definitions and techniques for culture. Other investigators have not used strict definitions of ventriculostomy-related infection, and some have not specified the method by which cerebrospinal fluid was collected from the ventriculostomy system.^{8,10,14}

Since there are no uniform criteria for diagnosis of ventriculitis or meningitis in the literature, we chose to define these infections microbiologically whether or not other signs of infection were present. In each case in which cerebrospinal fluid was obtained from both the ventricular catheter and a lumbar puncture, the same species with the same antibiotic sensitivity was recovered from both sites. In three patients the diagnosis of ventriculitis or meningitis was established by culture of cerebrospinal fluid obtained by lumbar puncture. In 9 of 11 patients in whom ventriculitis or meningitis was diagnosed only from cultures of cerebrospinal fluid aspirated from the ventricular catheter, the cultures yielded heavy growth or there were multiple positive cultures or the causative microor-

Table 2. Relation of Fever, Peripheral Leukocytosis, and Cerebrospinal-Fluid Pleocytosis to Ventriculitis or Meningitis.

SIGN	PATIENTS WITH VENTRICULITIS OR MENINGITIS *			PATIENTS WITHOUT VENTRICULITIS OR MENINGITIS			P VALUE
	NO. OF PATIENTS	SIGN PRESENT	SIGN ABSENT	NO. OF PATIENTS	SIGN PRESENT	SIGN ABSENT	
	no. of patients (%)			no. of patients (%)			
Fever	8 *	6 (75)	2 (25)	113	47 (42)	66 (58)	0.07 †
Peripheral leukocytosis	7 *	6 (86)	1 (14)	113	57 (50)	56 (50)	0.07 †
Cerebrospinal-fluid pleocytosis	18	14 (78)	4 (22)	52	12 (23)	40 (77)	0.0001 ‡

*Patients without infection at other sites.

†By Fisher's exact test.

‡By the chi-square test.

Table 3. Analysis of Risk Factors for Ventriculostomy-Related Infection.

RISK FACTOR	PATIENTS WITH VENTRICULITIS OR MENINGITIS		PATIENTS WITHOUT VENTRICULITIS OR MENINGITIS		P VALUE
	FACTOR PRESENT	FACTOR ABSENT	FACTOR PRESENT	FACTOR ABSENT	
	<i>number of patients (per cent)</i>				
Neurosurgical diagnosis					
Head trauma	10 (53)	9 (47)	108 (57)	81 (43)	0.71 *
With mass lesions ‡	4 (21)	15 (79)	26 (14)	163 (86)	0.28 †
Without mass lesions	6 (32)	13 (68)	82 (43)	107 (57)	0.32 *
Intracerebral hemorrhage	1 (5)	18 (95)	7 (4)	182 (96)	0.54 †
Intracerebral hemorrhage with intraventricular hemorrhage	3 (16)	16 (84)	5 (3)	184 (97)	0.027 †
Tumor	2 (11)	17 (89)	31 (16)	158 (84)	0.39 †
Tumor with intraventricular hemorrhage	1 (5)	18 (95)	1 (0.5)	188 (99.5)	0.17 †
Underlying diseases	6 (32)	13 (68)	60 (32)	129 (68)	0.99 *
Neurosurgical operation					
Ventricles entered	3 (23)	10 (77)	11 (15)	64 (85)	0.34 †
Ventriculostomy performed in intensive-care unit	12 (63)	7 (37)	148 (78)	41 (22)	0.12 †
Nafcillin prophylaxis	12 (63)	7 (37)	81 (43)	108 (57)	0.09 *
Intracranial pressure \geq 20 mm Hg	19 (100)	0 (0)	146 (80)	36 (20)	0.019 †
Cerebrospinal fluid drained	18 (95)	1 (5)	153 (81)	36 (19)	0.12 †
Duration of catheterization (>5 days)	9 (47)	10 (53)	41 (22)	148 (78)	0.017 †
Problems and manipulations					
Leaks	2 (11)	16 (89)	8 (5)	147 (95)	0.28 †
Disconnections	12 (67)	6 (33)	74 (47)	85 (53)	0.11 *
Change of syringes					
10 or 20 ml	2 (11)	16 (89)	47 (30)	108 (70)	0.09 *
Tuberculin	2 (11)	16 (89)	14 (9)	141 (91)	0.52 †
System component changes	5 (28)	13 (72)	22 (14)	133 (86)	0.125 †
Irrigation	9 (50)	9 (50)	37 (24)	119 (76)	0.021 †
Dressing changes	5 (28)	13 (72)	40 (26)	116 (74)	0.52 †
Gross blood in drainage system	13 (68)	6 (32)	75 (55)	62 (45)	0.26 *
Previous ventriculostomy	3 (16)	16 (84)	35 (19)	154 (81)	0.53 †
Other central-nervous-system instrumentation	6 (32)	13 (68)	67 (35)	122 (65)	0.74 *

*By the chi-square test.

†By Fisher's exact test.

‡Subdural hematoma, epidural hematoma, intracerebral hemorrhage.

ganism was also isolated from cerebrospinal fluid at autopsy. Thus, there is considerable evidence that these patients had ventriculitis or meningitis and not just contamination of cerebrospinal-fluid specimens.

Analysis of the relation of fever and peripheral leukocytosis to ventriculitis or meningitis was very difficult in our series of patients undergoing ventriculostomy, because many had infections at other body sites that are also commonly associated with fever and leukocytosis. When patients with infections at other sites were excluded from the analysis, few remained in the group with ventriculitis or meningitis. Thus, the P value of 0.07 may have reflected either a weak relation or an inadequate sample size. The borderline sig-

nificance was also reflected by the very low predictive values of fever and leukocytosis.

We found cerebrospinal-fluid pleocytosis in 14 of 18 patients (78 per cent) with ventriculitis or meningitis diagnosed on the basis of cultures. Thus, although the relation between pleocytosis and these infections was significant, 22 per cent of patients with infection did not have pleocytosis in response to the infection. This figure is high, considering the seriousness of the consequences of a delayed or missed diagnosis of ventriculitis or meningitis. Furthermore, a similar proportion (23 per cent) of patients without cultures indicating infection had pleocytosis. In this group pleocytosis may have reflected a foreign-body response to ventric-

ulostomy or a response to some central-nervous-system insult other than infection. Other authors have also reported pleocytosis in patients undergoing ventriculostomy in the absence of cultural evidence of ventriculitis or meningitis.^{11,12} These findings suggest that pleocytosis alone is insufficient for the diagnosis of ventriculitis or meningitis and that the best approach for diagnosis is culture of cerebrospinal fluid obtained by aspiration from the ventricular catheter or by lumbar puncture.

Several risk factors for ventriculostomy-related infection were identified in this study. Although most diagnoses were not significantly associated with ventriculostomy-related infection, the diagnosis of intracerebral hemorrhage with intraventricular hemorrhage was. Neurosurgical diagnoses in two other series of patients have been reported, but their relation to the occurrence of ventriculostomy-related infection was not examined.^{10,11} Although patients with intraventricular hemorrhage may need intracranial-pressure monitoring and cerebrospinal-fluid drainage for longer periods than other patients, in our series this diagnosis was significantly associated with ventriculostomy-related infection regardless of the duration of catheterization.

Another risk factor for ventriculostomy-related infection identified in our study was neurologic surgery. Sundbärg and co-workers noted that all the patients in their series who became infected had undergone a neurosurgical procedure.⁹ Although neurosurgical operations were associated with ventriculostomy-related infection in our patients, entry into the ventricles during surgery was not related to the occurrence of infection. Whether the ventricular catheter was inserted in the Neurosurgery Intensive Care Unit or in the operating room did not significantly alter the incidence of ventriculostomy-related infection. Thus, using our technique for insertion of ventricular catheters, we found no evidence that patients needed to be taken to the operating room for ventriculostomy.

Although patients were not randomly assigned to receive nafcillin prophylaxis, our data indicate that nafcillin did not influence the occurrence of ventriculostomy-related infection (Table 3). In the only previous study in which the effect of prophylactic antibiotics could be assessed, Wyler and Kelly noted fewer infections in their patients who received prophylactic antibiotics.¹⁰ However, unlike our study, theirs was retrospective, and antibiotics were given continuously while the ventricular catheter was in place.

An intracranial pressure of 20 mm Hg or higher was significantly associated with ventriculostomy-related infection in our patients, but drainage of cerebrospinal fluid was not. To our knowledge, the relation between intracranial pressure and ventriculostomy-related infection has not been studied previously. Like patients who have intraventricular hemorrhage, those with intracranial pressure of 20 mm Hg or more may need ventricular catheterization for longer periods than other patients. In our patients who had a catheter in

place for more than five days, intracranial pressure of 20 mm Hg or more remained significantly associated with infection.

Patients in our study who had a ventricular catheter in place longer than five days had a significantly increased risk of ventriculostomy-related infection. A life-table analysis revealed that the risk of infection increased dramatically after Day 5 and was 42 per cent by Day 11. Three previous studies have examined the relation between the duration of ventricular catheterization and the occurrence of ventriculostomy-related infection; two found no relation, and one found a higher risk of infection in patients whose catheter remained in place for a longer period.⁹⁻¹¹ All these studies were retrospective, which may account for the failure to demonstrate a significant association. Our finding that the duration of catheterization was an important risk factor for infection, in conjunction with our observation that previous ventriculostomies did not increase the risk of ventriculitis or meningitis associated with subsequent catheterization, provides strong support for routine removal of ventricular catheters after five days and if continuation of monitoring is indicated, placement of a new catheter at another site.

We found irrigation of the ventriculostomy system to be a significant risk factor for ventriculostomy-related infections. Irrigation has been mentioned in a previous report as a possible risk factor for infection, but the authors did not have sufficient data to prove or disprove a relation.¹⁰ It is possible that such a manipulation of the system results in infection because bacteria are introduced by touch contamination and subsequent retrograde migration of microorganisms up the fluid column and into the ventricles.

On the basis of data from our study, we make the following recommendations. First of all, when proper aseptic technique is used, ventricular catheters may be safely inserted in the intensive-care unit. Secondly, given the low predictive value of fever, leukocytosis, and pleocytosis, the diagnosis of ventriculitis or meningitis in patients who have undergone ventriculostomy should be made on the basis of cultures of cerebrospinal fluid obtained by aspiration through the ventricular catheter or by lumbar puncture. Thirdly, a ventricular catheter should be removed after five days. If monitoring is needed for a longer period, the catheter should be reinserted at a new site. In addition, a meticulous technique for maintaining the system should be used by all personnel directly involved with it. Finally, every effort should be made to limit irrigation of the system.

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HOMOZYGOUS PROTEIN C DEFICIENCY MANIFESTED BY MASSIVE VENOUS THROMBOSIS IN THE NEWBORN

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Abstract We studied a family in which two infants had died with massive venous thrombosis shortly after birth. Protein C antigen was undetectable by immunologic assays of plasma available from one infant. (Protein C is a potent naturally occurring anticoagulant that inactivates activated coagulation factors V and VIII.) The parents, who were first cousins, both had partial protein C deficiency. Reduced protein C levels were also observed in 12 of

25 additional family members. None of the partially deficient family members (age range, 4 to 70 years) had thrombotic episodes. Our data support the view that hereditary protein C deficiency is an autosomal disorder in which the homozygous state may be manifested by the virtual absence of plasma protein C and by fatal thrombosis in the neonatal period. (*N Engl J Med* 1984; 310:559-62.)

IN its activated form, the vitamin K-dependent plasma protein designated protein C functions as a potent anticoagulant that inactivates activated coagulation factors V and VIII.^{1,2} Protein C may also stimulate fibrinolysis.³ In 1981, Griffin et al.⁴ described a family in which three members who had plasma levels of protein C antigen between 38 and 49 per cent had venous thrombosis in early adult life. Since then, additional families with similarly affected members have been reported,⁵⁻⁹ suggesting that protein C has an important role in hemostasis and that even a moderate reduction in the plasma protein C level may be associated with an increased risk of thrombosis.

an autosomal disorder in which the homozygous state may be incompatible with survival beyond the neonatal period.

DESCRIPTION OF THE FAMILY

The pedigree of this family is shown in Figure 1. The family was of Arab-Israeli origin and from a village in the lower Galilee. The father and mother of the proband were first cousins.

Infants with Thrombosis

The proband, IV-6 (Fig. 1), was a female infant delivered in November 1982 by elective cesarean section. Her birth weight was 3100 g, and the Apgar score was 10/10₅. Vitamin K was not administered after birth. Macroscopic hematuria was noted several hours after birth, at which time a left abdominal mass was palpated. On the following day, a right abdominal mass was also felt, and a diagnosis of bilateral renal-vein thrombosis was made by means of ultrasound examination. In a blood sample drawn on the fourth day of life the platelet count was 130,000 per cubic millimeter, the activated partial thromboplastin time was 40.8 seconds (normal range, 38 to 55), the prothrombin time was 14.8 seconds (normal range, 11 to 13), the thrombin time was 15 seconds (control, 15 seconds), the fibrinogen level was 195 mg per deciliter (normal range, 200 to 400), and the euglobulin lysis time was two hours (control, two hours). The same blood sample was later found to be almost totally deficient in protein C antigen. The infant lived for only 34 days. Oliguric renal failure and bilateral chylothorax requiring repeated paracentesis were major clinical problems. The immediate cause of death was cardiac arrest.

Postmortem examination revealed extensive thrombosis involving the inferior vena cava, both renal veins, and both iliac veins.

We describe a family in which two infants died with massive venous thrombosis shortly after birth. Protein C antigen was virtually undetectable in plasma available from one infant. Both parents and 12 other family members had reduced levels of protein C antigen compatible with the heterozygous state. These observations indicate that hereditary protein C deficiency is

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