Original Article

Infection of Cerebrospinal Fluid Shunts: Causative Pathogens, Clinical Features, and Outcomes

Kuo-Wei Wang, Wen-Neng Chang[1], Teng-Yuan Shih, Chi-Ren Huang[1], Nai-Wen Tsai[1], Chen-Sheng Chang[2], Yao-Chung Chuang[2], Po-Chou Liliang[3], Thung-Ming Su, Cheng-Shyuan Rau, Yu-Duan Tsai[3], Ben-Chung Cheng[4], Pi-Lien Hung[5], Chin-Jung Chang[6] and Cheng-Hsien Lu[1]*

Department of Neurosurgery, [1]Neurology, [4]Medicine, and [5]Pediatric Neurology, Chang Gung Memorial Hospital-Kaohsiung, [2]Department of Neurology and [3]Neurosurgery, I-Shou University Hospital, Kaohsiung, and [6]Department of Pediatrics, Buddhist Dalin Tzu Chi General Hospital, Chia-Yi, Taiwan

SUMMARY: This retrospective chart review describes the clinical features, pathogens, and outcomes of 46 patients with cerebrospinal fluid (CSF) shunt infections collected over 16 years. The overall CSF shunt infection rate was 2.1%, broken down into 1.7 and 9.3% in adult and pediatric groups, respectively. Fever and progressive consciousness disturbance were the most prominent clinical features in the adult patient group, whereas disturbance of consciousness and abdominal symptoms and signs were the two most common clinical features in the pediatric patient group. The most frequently isolated microorganisms were of the *Staphylococcus* spp., including *Staphylococcus aureus* and coagulase-negative *Staphylococcus*, which accounted for 47% of the episodes. Furtheremore, increases in polymicrobial and Gram-negative bacilli infections were observed in our study. Due to the high proportion of oxacillin-resistant *Staphylococcus* spp. and polymicrobial infections, we recommend initial empirical antibiotics with both vancomycin and a third-generation cephalosporin for cases in which the causative bacteria has not been identified or for which the results of antimicrobial susceptibility tests are not available. For patients who develop smoldering fevers, progressive disturbed consciousness, seizures, or abdominal fullness after ventriculoperitoneal shunt procedures, CSF shunt infections should be suspected. Although some infections have been managed successfully with antimicrobial therapy alone, the timely use of appropriate antibiotics according to antimicrobial susceptibility testing and the removal of the shunt apparatus are essential for successful treatment.

INTRODUCTION

Postoperative infections of cerebrospinal fluid (CSF) shunts occur in 5-27% of cases in most neurosurgical units throughout the world (1-3). Although some infections have been managed successfully with antimicrobial therapy alone (4,5), the most frequently recommended method of treatment has been the removal of the shunt apparatus and the concomitant initiation of appropriate antimicrobial therapy (4,6). Despite the advent of modern neurosurgical techniques, new antibiotics, and modern imaging techniques, infection after ventriculoperitoneal (VP) shunt insertion and/or ventriculostomy is still a serious issue (7). Coagulase-negative staphylococci were once considered the most common type of pathogen encountered in cases of CSF shunt infection, accounting for 36-80% of the episodes in different reported series (4,6,8). In recent years, the widespread use of antibiotics and the increasing frequency of neurosurgical procedures may have changed the epidemiology of causative pathogens (9, 10). For a period of 16 years, we identified 46 patients with infections involving CSF shunts secondary to VP shunting and ventriculostomy procedures. The present study was undertaken to examine (i) the causative pathogens; (ii) the

clinical features relevant to shunt infections; (iii) the association between underlying conditions; and (iv) the therapeutic outcomes of our patients. This study was conducted in an effort to improve the therapeutic strategy employed for this type of potentially fatal central-nervous-system (CNS) infection.

MATERIALS AND METHODS

Using pre-existing standardized evaluation forms, we retrospectively reviewed the microbiological records for CSF and blood cultures, and the medical records of patients with bacterial meningitis admitted to Chang Gung Memorial Hospital (CGMH)-Kaohsiung between January 1986 and December 2001. CGMH-Kaohsiung is the largest medical center in southern Taiwan; this facility is a 2,482-bed acute-care teaching hospital, which provides both primary and tertiary referral care for patients.

At CGMH-Kaohsiung, there were 2,220 VP and ventriculostomy procedures performed during the study period. There were 2,112 patients in the adult group and 108 in the pediatric group. Forty-six cases with culture-proven CSF shunt infections were included in this study. For the comparative study, the patients were divided into two groups as follows: an adult group (>16 years old) and a pediatric group (<16 years old).

The criteria for a definite diagnosis of CSF shunt infection were established according to previous studies (11-15) and are listed in Table 1. Diphtheroids, coagulase-negative staphylococci, or propionibacteria isolated from the CSF were

*Corresponding author: Mailing address: Department of Neurology, Chang Gung Memorial Hospital, 123 Ta Pei Road, Niao Sung Hsiang, Kaohsiung Hsien, Taiwan. Tel: +886-7-731-7123 ext. 2286, Fax: +886-7-731-8762, E-mail: chlu99@ms44.url.com.tw

Table 1. Criteria for the diagnosis of CSF shunt infection

The criteria for CSF shunt infection include both of the following items:
(A) A positive cerebrospinal fluid (CSF) or CSF shunt tip culture in patients with clinical presentation of acute bacterial meningitis, or with signs or symptoms of shunt malfunction or obstruction;
(B) At least one of the following parameters of bacterial inflammation of the CSF:
(1) a leukocyte count of $>0.25 \times 10^9$/L with predominant polymorphonuclear cells;
(2) a CSF lactate concentration of >3.5 mmol/L;
(3) a glucose ratio (CSF glucose/serum glucose) of <0.4;
(4) a CSF glucose value of <2.5 mmol/L if no simultaneous blood glucose is observed.

considered etiologic agents only if found repeatedly or if cultured from the tip of an indwelling neurosurgical device (12). Relapse of a shunt infection was considered as an infectious episode, if it occurred within 3 weeks of the completion of therapy with an isolate that was of the same genus and species that which had as previously been isolated (7). A second episode of meningitis was considered as a recurrence if it was due to a different organism from the first organism, or if it was due to the same organism but occurred more than 3 weeks after the completion of therapy for the initial episode (12). Patients were considered to have mixed bacterial meningitis if at least two bacterial organisms were isolated from the initial CSF cultures (16). Patients excluded from this study were those who: i) only demonstrated positive cultures from vascular access or surgical sites, but with no isolation of pathogens from the CSF, and ii) only demonstrated one positive blood culture serving to establish the diagnosis of bacteremia, but with no isolation of bacterial pathogens from the CSF. Moreover, patients who were initially treated at other hospitals but subsequently moved to our hospital for further therapy were also included in this study, with the initial clinical and laboratory data collected at those hospitals used for the present analysis.

Appropriate antimicrobial therapy was defined as the administration of one or more antimicrobial agents shown to be effective against bacterial pathogens by susceptibility tests and capable of passing through the blood-brain barrier in an adequate amount (17). Antibiotic susceptibility was tested by the Kirby-Bauer disc diffusion method (BBL Muller-Hinton II agar; Becton Dickinson Microbiology Systems, Cockeysville, Md., USA). The Vitek System (VITEK®, bioMérieux Vitex, Hazelwood, Mo., USA), an established automated method of testing antimicrobial susceptibility with the ability to generate minimal inhibition concentration (MIC) data, was also used to further determine the antimicrobial susceptibility of bacterial pathogens. The MIC breakpoints are based on guidelines from the National Committee for Clinical Laboratory Standards (NCCLS). Susceptibility was indicated by the MIC value. If the cultures grew *Streptococcus pneumoniae*, an Etest method (AB BIODISK, Solna, Sweden) was also performed to further determine antimicrobial susceptibility. Leukocytosis was defined as a white blood cell count of greater than 15×10^9/L of peripheral blood. Bacteremia was defined as the isolation of bacterial pathogens from more than one blood culture.

RESULTS

The 46 patients with shunt infections included 36 adult patients (mean age: 50 years old; age range: 16 to 78 years)

and 10 pediatric patients (mean age: 925 days; age range: 10 days to 8 years) (Fig. 1). The overall infection rate was 2.1% (46/2,220), which was broken down into 1.7 and 9.3% for the adult and pediatric groups, respectively. The mean hospital stay was 26 ± 18.88 and 14 ± 4.43 days for the adult patients and pediatric patients, respectively. The underlying conditions of these 46 patients are listed in Table 2.

Pathogens isolated from the CSF cultures are listed in Table 3. A total of 42 patients had single episodes of CSF shunt infections. Four patients had more than one episode; two of these patients were included in the category "relapse of CSF shunt infection" and the other two cases were considered as a "recurrence of CSF shunt infection". Recurrence of CSF shunt infection occurred in two adult patients 3 weeks after the completion of therapy for the initial episode. One patient was infected *Escherichia coli*, followed by *Staphylococcus aureus* infection, and the other patient was infected *Enterobacter cloacae*, followed by *Citrobacter cloacae* infection. Relapse of CSF shunt infection occurred in two pediatric patients, and both of these cases were caused by *Staphylococcus epidermidis* infection. In the adult group, 80% of the cases involved a single pathogen, whereby *S. aureus* and coagulase-negative *Staphylococcus* were the most frequent pathogens, followed by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.
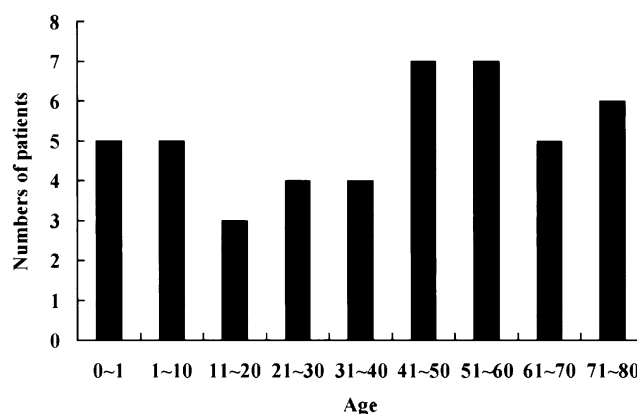

Fig. 1. Age distribution of patients with CSF shunt infection.

Table 2. Underlying conditions of patients[1]

	Adults $n = 36$	Children $n = 10$
ICH s/p craniotomy	11	0
Head trauma	8	0
Traumatic hydrocephalus	8	0
SAH s/p craniotomy	4	0
DM	4	0
ICH s/p ventriculostomy	4	0
ICH s/p V-P shunt	3	0
Head injury s/p craniotomy	2	0
Brain tumor s/p craniotomy	1	0
AVM s/p craniotomy	1	0
Prematurity	0	8
Congenital hydrocephalus	0	7
IVH with hydrocephalus	0	3
Cerebral palsy	0	3

[1]: 10 had more than one underlying diseases.
ICH=intracerebral hemorrhage, s/p= post status, DM=diabetes mellitus, SAH=subarachnoid hemorrhage, V-P=ventricular peritoneal; CSF=cerebrospinal fluid; EDH=epidural hemorrhage; SDH=subdural hematoma; AVM=arteriovascular malformation.

Mixed infections accounted for the other 20% of cases, in which *K. pneumoniae*, *E. coli*, *E. cloacae*, *Enterococcus* spp., *S. aureus*, *P. aeruginosa*, and coagulase-negative *Staphylococcus* were the implicated pathogens. In the pediatric group, 86% of the cases were infected by a single pathogen; with *S. aureus* and coagulase-negative *Staphylococcus* being the most prevalent. Among the 46 patients, 15 were identified as having antibiotic-resistant strains (Table 3). The 15 oxacillin-resistant *Staphylococcus* strains were *S. aureus* in 6 and coagulase-negative *Staphylococcus* in 9. The resistant strains in the latter 15 patients were resistant to penicillin, ampicillin,

oxacillin, and were only sensitive to vancomycin.

The clinical manifestations of the 46 patients are listed in Table 4. Progressive hydrocephalus, which was compared among previous neuroimaging findings, occurred in all of the patients. Abdominal symptoms such as poor intake, abdominal fullness, and vomiting were found in five pediatric patients. Seizure/or status epilepticus was observed in 11 patients, two of whom died. Septic shock occurred in seven patients, all of whom died. Two adult patients developed the syndrome inappropriate antidiuretic hormone (SIADH), and both of these patients died. Disseminated intravascular

Table 3. Causative pathogens in adult and pediatric shunt infection

Organisms	Adult group	Pediatric group	Total
1. Single episodes (*n* = 43)			
Staphylococcus spp.			
Staphylococcus aureus	7[1]	3[4]	10
Coagulase-negative *Staphylococcus*	7[2]	3[3]	10
Gram-negative bacilli			
Pseudomonas aeruginosa	4	1	5
Escherichia coli	3	0	3
Klebsiella pneumoniae	2	0	2
Citrobacter diversus	1	0	1
Non-A, B, D streptococci	1	0	1
Neisseria meningitidis	1	0	1
Enterococcus spp.	1	0	1
Mixed infection	7[5]	1[6]	8
2. Relapse (*n* = 2)	0	2[7]	2
3. Recurrence (*n* = 2)	2[8]	0	2

[1]: Five strains are resistant to oxacillin and penicillin.
[2]: Five strains are resistant to oxacillin and penicillin.
[3]: Two strains are resistant to oxacillin and penicillin.
[4]: One strain are resistant to oxacillin and penicillin.
[5]: *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter cloacae*, viridans streptococci, *Enterococcus*; *Enterococcus*, group D streptococci, coagulase-negative streptococci; *Pseudomonas aeruginosa*, *E. coli*, *Enterococcus*; coagulase-negative streptococci, *Staphylococcus aureus*; *P. aeruginosa*, *Acinetobacter baumannii*; *K. pneumoniae*, coagulase-negative streptococci; *Shewanella putrefaciens*, *P. aeruginosa*.
[6]: coagulase-negative streptococci, *S. aureus*.
[7]: Two *Staphylococcus epidermidis* strains are resistant to oxacillin and penicillin.
[8]: Recurrence of CSF shunt infection occurred to two adult patients 3 weeks after the completion of therapy for the initial episodes. One was infected *E. coli*, followed by *S. aureus* infection, and the other one was infected *E. cloacae*, followed by *Citrobacter cloacae* infection.

Table 4. Demographic features of patients

	Adults *n* = 36	Children *n* = 10
Mean Age	50 ± 14.29 (years)	925 ± 1013.66 (days)
Gender (male/female)	21/15	2/8
Clinical features		
Hydrocephalus	36	10
Fever	32	2
Disturbed consciousness	27	7
Seizure	11	0
Septic shock	7	0
SIADH	2	0
Disseminated intravascular coagulation	1	0
Abdominal signs	0	5
Outcomes		
Survived	28	10
Death	8[1]	0

SIADH=syndrome inapproriate antidiuretic hormone.
[1]: Five cases associated with infection, two cases associated with recurrent stroke, one case associated heart disease.

coagulation (DIC) was found in one patient, who also died.

Except for in seven patients, removal of the colonized shunt and revision was performed. As regards the antimicrobial therapy for all 46 patients, appropriate antibiotics were given to 41 patients, but not to the five remaining patients. All 41 patients who received appropriate antibiotic therapy survived. The latter five cases that had not received appropriate antimicrobial therapy died due to fulminant clinical courses that occurred before the final culture results were available.

At a follow-up of 6 months, 38 patients had survived, while the other eight had died (Table 4). Five patients among these eight patients died of septic shock. Two patients died of stroke and one died of cardiopulmonary failure not associated with an infectious condition. The overall mortality rate in the adult group was 14%, but no mortality was present in the pediatric group.

DISCUSSION

Shunts inserted for the treatment of hydrocephalus are quite susceptible to bacterial infection. The incidence of CSF shunt infection was approximately 2 - 22% in most neurosurgical units throughout the world (3,6). In our study, the infection rates were 2.1%. Several mechanisms are implicated in the development of CSF shunt infection. These include: (i) the presence of a foreign body, which seems to enhance the virulence of microorganisms (8,18-21); (ii) an immunological "vacuum," i.e., conditions essentially devoid of factors needed for bacterial destruction (3); and (iii) the presence of opportunistic microorganisms that are allowed to multiply unharmed (20). Although the incidence rate of the present study differed from those of other studies from western countries (22,23), if appears that there is an increasing prevalence worldwide in recent years. This trend may be due to the increasing number of neurosurgeries, increasingly active neurosurgical programs, and the increasing number of patients with head injuries due to motorcycle accidents.

Fever and progressive deterioration of consciousness were the consistent findings among our patients. Furthermore, acute abdominal symptoms such as abdominal fullness, vomiting, and poor appetite were especially present in our pediatric patients, but these symptoms were not as conspicuous in our adult group. Although early detection and diagnosis of shunt infection is usually difficult because of its nonspecific clinical features, if patients in a posttraumatic and postoperative state develop fever, and if they display progressive deterioration of consciousness and abdominal fullness, CNS shunt infection should be suspected. In such cases, an immediate neuroimaging and CSF studies should be performed to determine whether or not meningitis is indeed present.

Because of the nature of head trauma and neurosurgical procedures, the infectious pathogen in cases of adult shunt infection is likely to be a microorganism from the resident bacterial flora of the skin, the flora of the nasopharynx, or the external auditory canal. However, the possibility of nosocomial bacteria should not be ignored (24-27). Aspiration of gastric contents is common in unconscious patients and is frequently complicated by bacterial superinfection. The routine use of antacids and H2 blocking agents leads to bacterial colonization of the stomach with anaerobes and Gram-negative aerobes (24,28,29), which may account for why a large percentage (33%) of these infections are caused by enteric Gram-negative organisms. Furthermore, a relatively high proportion of mixed infections was detected in the present

study, i.e., mixed infections accounted for 19% (7/36) of the episodes in the adult group. These cases were frequently associated with head trauma and neurosurgical procedures as underlying conditions. Based on the present analysis, it appears that such infection among adults are more complicated and require more time to eradicate.

In our study, pediatric CSF shunt infection rates were the highest among patients in the first year of life. Although the exact causes for the rate increase in this age group are not known, children from 1 to 6 months of age have a greater susceptibility to shunt infection than previously thought, due to a relative deficiency in their immune response against bacteria (15). An alternative explanation for CSF shunt infection in the pediatric group would be based on age-related changes in the skin and its resident bacterial flora (23). The density of aerobic cocci and *Propionibacterium acnes* is higher in infancy than in early childhood. All of our pediatric patients had congenital hydrocephalus and most patients were born prematurely. Thus, there may be congenital immune deficiencies in such patients. Taken together, these explanations may account for the higher incidence of infection observed in the pediatric group than the adult group.

In our study, *Staphylococcus* spp., including *S. aureus* and coagulase-negative *Staphylococcus*, accounted for 80% (8/10) of the implicated pathogens in pediatric CSF shunt infections. A high incidence of infection with *Staphylococcus* spp. has also been noted in other studies (22,30). In our study, cases of multi-antibiotic resistant strains accounted for 33% (15/46) of the episodes, all of which were oxacillin-resistant *Staphylococcus* strains.

In our hospital, the control of infection with resistant bacteria strains is based on a slightly modified version of the "Guideline for Isolation Precautions in Hospital" from the Centers for Disease Control and Prevention (CDC). A sample instruction card was provided for posting on affected patients' room doors, including the following recommendations for source isolation: i) hands must be washed with detergent before leaving the patient's room; ii) single isolation rooms are necessary, and patients must obtain permission to leave the room; iii) masks are not indicated, unless there is contact with infected secretion; iv) gloves are required for direct contact with infected tissues; and v) the infected patients are cared for by the same nursing team. Despite this isolation procedure, the findings of the present study indicate a high proportion of oxacillin-resistant *Staphylococcus* spp. in CSF shunt infections in recent years.

In conclusion, CSF shunt infections have become an important issues in cases of bacterial meningitis in the hospital setting. The predisposing factors, causative pathogens, and outcomes differ between adult and pediatric cases. Cases among adults commonly followed head trauma and postneurosurgical states; fulminant course and fatalities were observed in this group, which also required more time for treatment. In contrast, pediatric cases commonly followed premature delivery and involved both a more indolent course and a more favorable outcome. *Staphylococcus* spp., Gram-negative bacilli, and polymicrobial infections were the predominant causative pathogens in adult patients. Only the *Staphylococcus* spp. were common in our pediatric patients. Due to the high proportion of oxacillin-resistant *Staphylococcus* spp. and polymicrobial infection, we recommend initial empirical antibiotic treatment with both vancomycin and a third-generation cephalosporin, provided the causative bacteria has not been identified or when the results of anti-

microbial susceptibility tests are not available. In patients who develop smoldering fevers, progressive disturbed consciousness, seizures, or abdominal fullness after VP shunt procedures, CSF shunt infections should be suspected. Immediate neuroimaging and CSF studies should be undertaken in order to determine whether CSF shunt infection is indeed present. The guidelines for shunt infection include early discovery and an early treatment. Removal of the infected shunt and the use of appropriate antibiotics are standard therapeutic approaches in cases of CSF shunt infection; these interventions are essential for the survival of patients with this type of infection.

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