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Aseptic Meningitis in Adults and Children: Diagnostic and management challenges

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Abstract

Background—Aseptic meningitis represents a common diagnostic and management dilemma to clinicians.

Objectives—To compare the clinical epidemiology, diagnostic evaluations, management, and outcomes between adults and children with aseptic meningitis.

Study Design—We conducted a retrospective study from January 2005 through September 2010 at 9 Memorial Hermann Hospitals in Houston, TX. Patients age ≥ 2 months who presented with community-acquired aseptic meningitis with a CSF white blood cell count >5 cells/mm³ and a negative Gram stain and cultures were enrolled. Patients with a positive cryptococcal antigen, positive blood cultures, intracranial masses, brain abscesses, or encephalitis were excluded.

Results—A total of 509 patients were included; 404 were adults and 105 were children. Adults were most likely to be female, Caucasian, immunosuppressed, have meningeal symptoms (headache, nausea, stiff neck, photophobia) and have a higher CSF protein ($P < 0.05$). In contrast, children were more likely to have respiratory symptoms, fever, and leukocytosis ($P < 0.05$). In 410 (81%) patients, the etiologies remained unknown. Adults were more likely to be tested for and to have *Herpes simplex virus* and *West Nile virus* while children were more likely to be tested for and to have Enterovirus ($P < 0.001$). The majority of patients were admitted (96.5%) with children receiving antibiotic therapy more frequently ($P < 0.001$) and adults receiving more antiviral therapy

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CONFLICT OF INTEREST:

No competing interests for BS, LS, EA, SH, QK. RH is a consultant to bioMérieux and is part of the speaker's bureau for the Medicine's company, Merck, Pfizer and Biofire diagnostics.

Ethical Approval:

The study was approved by the University of Texas Medical School at Houston Committee for the Protection of Human Subjects and by the Memorial Hermann Hospital Research Review Committee.

($P=0.001$). A total of 384 patients (75%) underwent head CT scans and 125 (25%) MRI scans; all were normal except for meningeal enhancement. All patients had a good clinical outcome at discharge.

Discussion—Aseptic meningitis in adults and children represent a management challenge as etiologies remained unknown for the majority of patients due to underutilization of currently available diagnostic techniques.

Keywords

aseptic meningitis; children; adults; diagnosis; treatment

INTRODUCTION

Aseptic meningitis is defined as an acute community-acquired syndrome with cerebrospinal fluid (CSF) pleocytosis in the absence of a positive Gram stain and culture, without a parameningeal focus or a systemic illness, and with a good clinical outcome [1]. This case definition has remained relatively unchanged since its initial description in 1925 by Wallgren. The clinical syndrome has since been further characterized and understood to include multiple types of infectious and non-infectious etiologies, although up to 71% of those cases remain with uncertain etiology, especially when PCR testing is not completed. [2]. The most common etiologies of aseptic meningitis in the United States (US) are viruses such as Enterovirus, Herpes simplex type 2, and West Nile virus. Varicella zoster virus and Cytomegalovirus have also been described as causes of aseptic meningitis [2]. Several prior studies have sought to develop clinical models to try to differentiate this diagnosis from other urgent treatable conditions such as bacterial meningitis and encephalitis [3–4]. To standardize the case definition, a recent international working group defined aseptic meningitis as patients with meningitis symptoms, a CSF white cell count of >5 cells/mm³, and a negative CSF Gram stain [5]. The diagnostic certainty of this syndrome was further stratified into three levels: Level 1 if the patient had negative CSF cultures without previous antibiotic exposure, Level 2 with negative CSF cultures with previous antibiotic therapy and Level 3 with concomitant encephalitis.

Despite such tools, evaluation of this clinical syndrome in the present day clinical setting remains variable representing a diagnostic and management dilemma to clinicians. As such, the purpose of this study was to characterize and compare the baseline characteristics, management strategies, etiologies of adult and pediatric patients with aseptic meningitis and to uncover the frequency and yield of the use of available diagnostic techniques and cranial imaging in this syndrome.

METHODS

Study Design & Case Definitions

A retrospective observational cohort study was completed spanning from January 2005 through September 2010. Cases were defined in a similar method to those cited by Tapiainen et al using only Level 1 and 2 diagnostic certainties [5]. Patients above 2 months of age presenting to the emergency department from the community with acute symptoms of

meningitis, CSF white cell count of >5 cells/mm³, negative Gram stain and culture, and no identified parameningeal focus of infection were included by reviewing all cases with an ICD9 discharge code of meningitis. The cohort was composed of patients presenting to nine Memorial Hermann hospitals, all within the greater Houston metropolitan area. Patients aged 18 years or older were considered adults for the purposes of this study. Baseline patient characteristics at time of presentation to the emergency department, use of microbiologic and imaging modalities, and Glasgow outcome scores [6] at time of discharge were evaluated. The study was approved by the University of Texas Medical School at Houston Committee for the Protection of Human Subjects and by the Memorial Hermann Hospital Research Review Committee.

Statistical Assessment

Comparisons of baseline and clinical characteristics were made between pediatric and adult patients using the chi square test for categorical variables and ANOVA for continuous variables with significance attributable at $P<0.05$. All statistical analysis was completed using SPSS for Mac version 21 (SPSS, Chicago, IL, USA).

RESULTS

We identified a total of 907 adults and children with meningitis above the age of 2 months. We excluded 398 patients for the following reasons: positive Gram stain for bacteria or yeast ($n=113$), nosocomial meningitis ($n=101$), encephalitis presentation ($n=86$), and positive CSF or blood culture ($n=84$), and incomplete medical records ($n=14$). A total of 509 patients met the inclusion criteria. Figure 1 shows the age distribution for all the cases in decades with the majority of patients being between 20 and 40 years old. Figure 2 shows the distribution by month of presentation with the most common time between May and October. As shown in Table 1, adults composed the majority of patients at 404 (79%) while 105 (21%) patients were children; the median age in the adults was 34 years (18–89) and in the pediatrics it was 4.9 years (2 months–17 years of age). The majority of patients were 20–40 years old (see Figure 1). Male gender was more common in pediatric patients (59% vs 42%, $P=0.002$). There were also significant differences in the ethnicity with adults and children having more Caucasian and Hispanics, respectively ($p<0.001$). More adults were immunocompromised than children (22.5% vs 4.7%, $P<0.001$). Previous antibiotic therapy was used more commonly in pediatrics than adults (37.1% vs. 7.2%, $P<0.001$). The majority of the patients with aseptic meningitis presented between the months of May and October (see Figure 2).

There were several differences between adults and children in the baseline clinical and laboratory presentations (see Table 1). Adults were more likely than children to complaint of headache, nausea or vomiting, stiff neck, malaise, photophobia, and have nuchal rigidity present on exam ($p<0.05$). Fever, concurrent respiratory illness, and rash were more commonly seen in the pediatric population ($p<0.05$). On initial CSF evaluation, adult patients had a trend to have a higher CSF WBC count ($p=0.066$) and also had higher CSF protein ($p<0.001$) than the pediatric group. Children also had higher median CSF neutrophilic pleocytosis than adults ($P<0.001$). Children had higher serum leukocyte counts than adults ($p<0.001$).

Diagnostic testing differed between adults and children (see Table 2). Adults were more commonly tested for HIV (30% vs. 5.7%, $P < 0.001$) with only 10 (8.1%) of adults testing positive for HIV. Virological studies such as polymerase chain reaction (PCR) for *Herpes simplex virus* (HSV), Enterovirus and *Varicella Zoster virus* (VZV) and serologies for *West Nile virus* (WNV) were done in the minority of patients. Out of the 509 patients in the cohort, only 175 (34.4%) had PCR for HSV sent, 165 (32.4%) for WNV studies, 138 (27.1%) for enterovirus PCR, 6 (1.2%) for VZV PCR, and 1 patient each for *Cytomegalovirus* (CMV) and *Mycoplasma pneumoniae* PCR. Furthermore, 182 (35.8%) of the patients had no viral studies sent at all. When done, the yield of an enterovirus PCR was 35.5% and for HSV PCR it was 20.6%. The overall yield of a West Nile serology was 4.8% (8 out of 96 (8.3%) cases in the West Nile season between June and October and 0 out of 69 (0%) between November and May) and all positive cases were adults. Adults were more likely to have testing for HSV ($p < 0.001$) and West Nile virus ($p = 0.001$) while pediatric patients were more likely to have testing completed for enterovirus ($p = 0.036$). Children were more likely to have at least one viral study (CSF PCR or arboviral serology) sent compared to adults (75.2% vs 61.3%, $P = 0.008$) and also were less likely to have an unknown infectious etiology (60.9% vs 85.6%, $P < 0.001$). Overall only 94 (18.5%) patients out of the total study had an infectious etiology identified [Enterovirus ($n = 49$), *Herpes simplex virus* ($n = 36$), *West Nile virus* ($n = 8$), *Varicella Zoster virus* ($n = 1$)].

As shown in Table 3, the majority of patients (96.5%) were admitted to the hospital for a median duration of 4 days (range 1–34 days). Empiric antibiotic therapy was given to the majority of patients (77.4%) with children receiving them more frequently than adults (92.3% vs 73.5%, $p < 0.001$). Empiric antiviral therapy with acyclovir was administered in 17.1% of the patients and was given more frequently in the adult population (19.8% vs 6.6%, $p = 0.001$). A computerized tomography (CT) scan of the head was performed in 384 (75%) patients and 125 (25%) patients had a magnetic resonance imaging (MRI) of the brain. Adults were more likely than children to have a CT scans and MRI of the brain done ($p < 0.001$). Of the CT scans completed, none showed significant abnormalities and only 11 (8.8%) of the MRI scans with contrast showed some meningeal enhancement. All patients in the retrospective cohort had a good outcome based on Glasgow outcome scale.

DISCUSSION

To our knowledge, this is one of the largest cohort studies of aseptic meningitis to date and the first one to compare adults and children. In our study, children were less likely to present with meningeal complaints (e.g., headache, stiff neck, nausea, photophobia) than adults. This is consistent with other studies where children more often present with a nonspecific febrile illness without meningismus [2]. Children were also most likely to present with fever, respiratory symptoms, and leukocytosis and to be exposed to previous antibiotic therapy before lumbar puncture. Even though approximately one third of children received antibiotic therapy, the majority were not treated for partially treated bacterial meningitis as the median length of stay and antibiotic therapy was 3 days. The etiology was not revealed in 81.5% in our study, while other series which performed PCR for the most common viral etiologies reported less proportion of unknown etiologies (50–70%) [7–9]. This low yield could in part be explained by underutilization of PCR for the most common viruses and for arboviral

serologies in real-life practice [10]. We think that tools to diagnose viral meningitis may be underutilized due to the generally benign course of illness with physicians primarily concerned with ruling out bacterial meningitis. We believe testing for viruses in aseptic meningitis is important as it may help clinicians avoid hospitalization, reduce length of stay in those admitted and reduce the use of empirical antimicrobial therapy. Even though when they were completed, they had a high yield in identifying a significant number of enterovirus and HSV cases in pediatric and adult cases, respectively. Identifying HSV as the most common etiology in adults was unusual despite the low proportion of patients tested. These viruses have also been found to be the most common etiologies in other series as well [6–9]. Several reports from Europe [7,8] and Asia [9] have now revealed that VZV it is the second most common leading cause of ASM even in the absent of skin lesions (*Zoster sine herpette*). In our study, only 1.2% of patients underwent a CSF VZV PCR making this an underdiagnosed etiology. Furthermore, it is also unclear the impact that VZV vaccination in childhood and Zoster vaccine in adults might have on the impact on the incidence of VZV meningitis.

In addition, checking WNV serology should be done during the endemic season (June through October) to enhance the diagnostic yield. [9] Additionally, only 25% of all patients with aseptic meningitis had an HIV serology done. Although we do not have a HIV PCR data from the serum or CSF, it is worth to mention that acute HIV infection could present as ASM and it has been overlooked from most of the major ASM series. A retrospective study revealed 3.4% of the remaining CSF tested positive for high HIV viral load in CSF. [10] Furthermore, we do not have PCR data for bacterial pathogens and therefore under-detection of culture-negative bacterial meningitis would be another limitation of this study.

The underutilization of PCR likely keeps infectious etiologies from being uncovered in a large majority of cases. When completed, they helped identify a significant number of enterovirus and HSV cases. This is concerning as it suggests that epidemiologic studies on infectious etiologies of aseptic meningitis are likely confounded by underuse of this diagnostic tool. In other studies, enterovirus and herpes viruses have also been cited as common etiologic agents. [10,11, 12,13] Furthermore, choice of PCR testing varies between adult and pediatric patients and these differences may well be due to paucity of sound epidemiologic studies. With the introduction of rapid multiplex PCR machines, this will likely change in the future.

Cranial imaging is commonly used in ASM and it is not helpful as all the scans were normal and did not alter management. A recent study [15] documents the lack of adherence of clinicians to the Infectious Diseases Society of America guidelines and confirms the lack of utility of obtaining cranial imaging in the absence of specific indications. Additionally, the majority of patients were admitted to the hospital and received empiric antibiotic therapy until CSF cultures were finalized as negative. Our study also confirms recent findings that viral meningitis can present with neutrophilic pleocytosis that is more common in children with enterovirus infection [16]. Identifying viral causes with a rapid PCR test could potentially avoid or decrease the length of stay in the majority of cases [17]. Overall, we found that the original definition of aseptic meningitis still holds true as does the assertion that patients afflicted with this disease process have generally good outcomes, aside from

possible neuropsychological sequelae, despite the diagnostic and treatment choices done by clinicians.

Our study had several advantages from previous work. First, this is the largest aseptic meningitis study done to date in the US since the 1960's. Second, this is the only study comparing adults and children with aseptic meningitis. Lastly, this study is also the largest study documenting the underutilization of currently available diagnostic techniques in this syndrome.

Despite the strengths, there are several limitations to this study. First, approximately one third of children had previous antibiotic therapy and could have had partially treated bacterial meningitis (Level 2 aseptic meningitis criteria). This would be unlikely as all the patients with or without antibiotic exposure had a good clinical outcome and the median length of intravenous antibiotic therapy was 3 days. Second, we did not account for non-infectious etiologies for aseptic meningitis such as adverse effects of medications, chemotherapy, or vaccines. Third, we did not analyze if there was an increase in the use of PCR during the study period and it is possible that the use of molecular tests has now increased. Finally, as our cohort was limited to patients admitted to a several hospitals in Houston, Texas the diagnostic practices and findings in aseptic meningitis have to be generalized in other populations.

CONCLUSIONS

Aseptic meningitis represents a diagnostic challenge as the majority of patients have unknown etiologies. Available diagnostic studies such as West Nile virus serologies and PCR for Enterovirus and Herpes simplex viruses are being underutilized and the majority are hospitalized and treated empirically with intravenous antibiotic therapy. Aseptic meningitis continues to be associated with a benign clinical outcome.

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Highlights

- Aseptic Meningitis have unknown etiologies in 81% of patients
- Currently available virological tools are underutilized.
- The majority of patients undergo unnecessary cranial imaging and antibiotic therapy.
- All patients had a good clinical outcome.

Figure 1.
Age distribution in years of 509 adults and children with Aseptic Meningitis.

Figure 2.
Distribution by month of year of 509 Adults and Children with Aseptic Meningitis.

TABLE 1

Baseline Characteristics, clinical presentations, and laboratory results in 509 Adults and Children with Aseptic Meningitis.

Variable	Adults (n=404)	Children (n=105)	Total (n=509)	P Value ^a
Median Age, years (range)	34 (18–89)	4.9 (0.17–17)	30 (0.17–89)	<0.001
Male gender, n (%)	171 (42.3)	62 (59)	233 (45.8)	0.002
Ethnicity, n (%)				<0.001
White	198 (49)	21 (20)	219 (43)	
African American	101 (25)	26 (24.7)	127 (24.9)	
Hispanic	91 (22.5)	55 (52.4)	146 (28.7)	
Asian	14 (3.4)	3 (2.8)	17 (1.9)	
Immunosuppressed ^b , n (%)	91 (22.5)	5 (4.7)	96 (18.9)	<0.001
Previous antibiotic therapy, IV or PO ^c n (%)	27 (6.6)	39 (37.1)	66 (12.9)	<0.001
Presenting Symptoms, n (%)				
Headache	399 (98.8)	63 (60)	462 (90.8%)	<0.001
Nausea or vomiting	302 (74.8)	67 (63.8)	369 (72.5)	0.02
Stiff neck	207 (51.2)	25 (23.8)	232 (45.6%)	<0.001
Photophobia	187 (46.3)	28 (26.7)	215 (42.2%)	<0.001
Malaise/Weakness	142 (35.1)	7 (6.7)	149 (29.3)	<0.001
Respiratory symptoms	46 (11.4)	33 (31.4)	79 (15.5)	<0.001
Presenting Signs, n (%)				
Temperature > 100.4 F	93 (23)	91 (86.7)	184 (36.1)	<0.001
Nuchal Rigidity	125 (30.9)	13 (12.4)	138 (27.1)	<0.001
Normal neurological exam ^d	404 (100)	105 (100)	509 (100)	1
Vesicular or petechial rash	6 (1.5)	5 (4.7)	11 (2.1)	0.004
Laboratory results, n (%)				
Median CSF leukocyte count (<i>cells/μl</i>), range	162.5 (6–10,100)	109 (4.9–49,000)	150 (4.9–49,000)	0.066
Median CSF mononuclear count (<i>cells/μl</i>), range	74 (12–100)	78 (8–98)	76 (8–100)	0.456
Median CSF polymorphonuclear count (<i>cells/μl</i>), range	21 (0–88)	14 (3–92)	17 (0–92)	0.321
Median CSF protein (<i>mg/dL</i>), range	70 (18–706)	44 (15–300)	66 (15–706)	<0.001
Median CSF glucose (<i>mg/dL</i>), range	57 (23–366)	58.5 (30–98)	57 (23–366)	0.951
Median serum leukocyte count ($10^3 \times \text{cells}/\mu\text{l}$), range	8.4 (0.9–42)	12.4 (3.1–46.5)	9.0 (0.9–46.5)	<0.001

^aP value comparing adult and pediatric cohorts

^b Human immunodeficiency virus, chronic steroid recipients, status post recent (< 1month) chemotherapy, or solid or bone marrow transplant recipients.

^c intravenous or oral antibiotic therapy

^d Glasgow Coma scale =15 and no focal neurological deficits or seizures

TABLE 2

Diagnostic Testing in 509 Adults and Children with Aseptic Meningitis *

Laboratory test	Adults (n=404)	Children (n=105)	Total (n=509)	P value ^a
HIV serology done	123 (30.0)	6 (5.7)	129 (25.3)	<0.001
HIV serology positive	10 (8.1)	0 (0)	10 (7.7)	0.001
Herpes simplex virus PCR ^b done	158 (39.1)	17 (16.2)	175 (34.4)	<0.001
Herpes simplex virus PCR positive	36 (22.8)	0 (0)	36 (20.6)	0.016
West Nile virus serologies done	150 (37.1)	15 (14.3)	165 (32.4)	0.001
West Nile virus positive	8 (5.3)	0 (0)	8 (4.8)	N/A
Enterovirus PCR done	60 (14.9)	78 (74.3)	138 (27.1)	<0.001
Enterovirus PCR positive	9 (15)	40 (51.3)	49 (35.5)	<0.001
Varicella Zoster virus PCR done	4 (1)	2 (1.9)	6 (1.2)	0.36
Varicella Zoster virus PCR positive	1 (25)	0 (0)	1 (16.7)	0.667
Other PCR done ^c	0 (0)	2 (1.9)	2 (0.3)	0.206
Other PCR positive	0 (0)	0 (0)	0 (0)	N/A
At least one viral study done	248 (61.3)	79 (75.2)	327 (64.2)	0.008
Unknown etiology ^d	350 (86.6)	65 (61.9)	405 (81.5)	<0.001

* All values in parenthesis represent percentages of total or percentages percentage of positive test results of total tests completed.

^aP value comparing adult and children cohorts;

^b polymerase chain reaction;

^cCytomegalovirus (1), *Mycoplasma pneumoniae* (1);

^d Adults: Known etiologies: HSV (36); Enterovirus (9); West Nile virus (8); Cytomegalovirus (1), *M. pneumoniae* (1); Children: Enterovirus (40).

TABLE 3

Management Decisions in 509 Adults and Children with Aseptic Meningitis.

	Adults (n=404)	Children (n=105)	Total (n=509)	P value ^a
Management Decisions, n (%)				
Admission to the Hospital	386 (95.6)	105 (100)	491 (96.5)	0.769
Median duration of hospitalization, days (range)	4 (1–34)	3 (1–33)	4 (1–34)	0.210
Empiric Antibiotic therapy	297 (73.5)	97 (92.3)	394 (77.4)	<0.001
Empiric Acyclovir therapy	80 (19.8)	7 (6.6)	87 (17.1)	0.001
Head CT ^b scan done	349 (86.3)	35 (33.3)	384 (75.4)	<0.001
Normal	100 (0)	100 (0)	100 (0)	N/A
MRI ^b of Brain done	115 (28.5)	10 (9.5)	125 (24.5)	<0.001
Meningeal enhancement	9 (7.8)	2 (20)	11 (8.8)	N/A
Adverse clinical outcome ^c	0 (0)	0 (0)	0 (0)	N/A

^aP value comparing adult and pediatric cohorts^bCT: Computerized Tomography; MRI: Magnetic Resonance Imaging^cGlasgow outcome scale from 1–4.