Etiology of Central Nervous System Infections in the Philippines and the Role of Serum C-Reactive Protein in Excluding Acute Bacterial Meningitis

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ABSTRACT

Objectives: The value of measurements of serum C-reactive protein (CRP) in differentiating central nervous system (CNS) infections of varying etiologies in the Philippines was investigated.

Methods: A wide array of bacteriologic and virologic methods as well as computed tomography, typical clinical presentation, and autopsy were used for etiologic diagnosis.

Results: Among 103 patients with CNS infection, etiology was identified in 60 (58%) cases. Bacteria were found in 19 (including 7 *Streptococcus pneumoniae*, 5 *Haemophilus influenzae*, 3 *Neisseria meningitidis*), tuberculosis in 4, viruses in 38 (including 20 coxsackievirus, 8 measles, 4 adenovirus, and 4 poliovirus infections), and brain abscess in 3 patients. C-reactive protein was elevated on admission in all 18 cases of bacterial meningitis tested, exceeding 50 mg/L in 17 (94%), and was not affected by prior antibacterial treatment. The mean CRP was significantly higher in the bacterial group than in the viral group (207 ± 111 mg/L vs. 39 ± 34 mg/L; $P < 0.001$). In the viral group one third had CRP above 50 mg/L. In patients with tuberculous meningitis, brain abscess, or cryptococcal meningitis, CRP was moderately to highly elevated.

Conclusions: In the presence of a normal CRP concentration (below 10 mg/mL) acute bacterial meningitis is excluded even in a developing country setting and antimicrobial therapy is not warranted.

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In the Philippines, meningitis is the ninth leading cause of mortality among infants.[1] Fatal outcome of bacterial meningitis in children in developing countries is twice as high as in developed countries (8.1% vs. 4.8%).[2] *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis* appear to be the three most common bacteria causing meningitis after the neonatal period both in developed and in developing countries.[3] However, owing to the lack of well-equipped bacteriologic laboratories the specific diagnosis of bacterial meningitis can seldom be ascertained in developing countries. Surprisingly little is known about the viral etiology of central nervous system (CNS) infections in developing countries. In a report from India, one fourth of 394 patients with "acute unexplained encephalopathy" had definite or probable evidence of viral etiology.[4]

Serum C-reactive protein (CRP) is an acute phase protein that is easy to measure and is known to be elevated in patients with bacterial meningitis.[5,6] Serum CRP has been used successfully in developed countries in the differential diagnosis of bacterial and viral meningitis.[7] Its applicability also has been tested in developing countries, to differentiate acute bacterial, from aseptic meningitis.[8,9] However, specific viral etiology was not determined in these studies and aseptic meningitis was defined as meningitis with negative bacterial cultures combined with recovery without antibiotic treatment. Furthermore, tuberculosis and brain abscess, which may be difficult to differentiate from bacterial or viral meningitis on clinical grounds, could confound the use of serum CRP in clinical practice.

The aim of this study was to evaluate the value of serum CRP in differentiating CNS infections with different types of etiology in patients with varying clinical presentations, in the Philippines. In addition to bacterial diagnostics, viral cultures and viral serology were used

for determining the specific viral etiology in a developing country setting.

MATERIALS AND METHODS

Patients

This study was conducted at the Research Institute for Tropical Medicine (RITM), Department of Health, Manila, Philippines. The catchment area for RITM consists of peri-urban slums and middle-class housing in southern Manila. From October 19, 1983, through November 16, 1984, all patients with symptoms suggestive of a CNS infection were evaluated for this study (n = 152). In 45 patients the CSF analysis was either normal or not available; or the clinical information did not support the diagnosis of encephalitis. In four cases the patient charts could not be retrieved for obtaining sufficient clinical data, and they were excluded from further analysis. Thus, the final group consisted of 103 patients with a CNS infection. Ninety-one patients had pleocytosis ($\geq 5 \times 10^6$/L) in the cerebrospinal fluid (CSF), one had a positive CSF bacterial culture (*S. pneumoniae*) without CSF leucocyte determination, and seven had clinical presentation compatible with encephalitis without CSF pleocytosis. Two patients had positive CSF viral cultures (echo 9 and an untyped enterovirus) without CSF pleocytosis. Another two patients without CSF analysis had a brain abscess, detected by a computed tomography (CT), or tuberculous meningitis, proven by autopsy. The study protocol was approved by the Internal Review Board of RITM.

Samples

Blood samples were drawn for bacterial cultures (n = 95 patients), CRP (n = 94), and glucose determinations (n = 80). Paired serum specimens were collected for coxsackievirus B (n = 57), poliovirus, mumps, herpes simplex, adenovirus, measles and cytomegalovirus antibody determinations (n = 76). Serum samples were stored at -20°C and transported in dry ice to Finland for viral antibody determinations. Cerebrospinal fluid samples (99 samples; 83 taken on admission) were collected for cell count, protein, and glucose determinations as well as for Gram stain (n = 97), bacterial (n = 98) and viral cultures (n = 43), and bacterial antigen detection (n = 39).

Method

Serum C-Reactive Protein Determination

Serum CRP determinations were carried out with an immunochemical assay using specific anti-CRP antiserum (Orion Diagnostica, Espoo, Finland) and turbidity measurement with a Shimazu UV-190 spectrophotometer at wavelength 340 nm.[10] C-reactive protein concentrations below the detection limit (10 mg/L) were taken as 1 mg/L, for calculations.

Blood and Cerebrospinal Fluid Culture

Venous blood (1 or 2 mL), obtained from two different sites was inoculated into 20 mL of brain-heart infusion broth supplemented with sodium polyanethol sulfonate (SPS). After overnight incubation, the broth was subcultured onto blood agar plates (BAP) with and without gentamicin, chocolate agar plates with and without bacitracin, and on MacConkey agar. Subcultures were done after 18 hours and on days 3, 5, 7, and 10. Isolated bacteria were identified by standard methods.[11]

A portion of CSF sample was inoculated onto a BAP or a trypticase soy agar (TSA) plate containing 5% sheep blood, a chocolate agar plate (CA), MacConkey agar, and trypticase soy broth (TSB). The BAP, TSA, and CA plates were incubated in a 5% CO_2 incubator at 35°C to 37°C, MacConkey agar and TSB at 37°C. Gram stain and India ink smears were performed.

Bacterial Antigen Detection

Latex Agglutination Test. A drop of CSF supernatant previously heated at 100°C for 5 minutes was placed on a card and mixed with a latex suspension sensitized with specific antisera for *S. pneumoniae, H. influenzae* type b, and *N. meningitidis* A, B, and C (Wellcogen, MUREX Diagnostics Ltd., Dartford, England). Agglutination was read within 2 minutes.

Counterimmunoelectrophoresis. Eight microliters of the CSF sample and 8 μL of each antiserum (polyvalent for *H. influenzae* a, b, c, d, e, and f, OMNI for *S. pneumoniae,* and *N. meningitidis;* DIFCO Laboratories, Detroit, Michigan, USA) were placed in adjacent wells, and electric current was applied through the diffusion medium. A visually detectable precipitation line between the wells (sample and antiserum) indicated a positive reaction.

Viral Culture

One to two hundred microliters of CSF specimen was inoculated into duplicate tube cell cultures of confluent monolayers of HEp-2, LLC-MK2, and HEL (human embryonic lung) cells and incubated in a roller drum at 35°C. Microscopic observation was done daily for 14 days with media change every 5 to 7 days. Cultures showing cytopathic effects (CPE) were analyzed further, and viruses were identified by indirect immunofluorescence test (IF), using virus-specific polyclonal antibodies (Denka Seiken Ltd., Japan) or by neutralization test for enteroviruses (Denka Seiken Ltd.).

Viral Antibodies

Enzyme immunoassay (EIA) for cytomegalovirus, poliovirus, measles, mumps, herpes and adenovirus antibodies was carried out as previously described.[12,13] Cytomegalovirus-coated microtiter plates were obtained from Labsystems, Helsinki, Finland. Purified viruses or viral antigens were used to coat polystyrene microtiter plates (5 μg of protein/mL) in phosphate buffered saline (PBS), pH 7.2 overnight at 4°C. A twofold or a higher increase in the endpoint titer values was considered diagnostic.[13]

In IgM antibody assay, the limit for a positive result was calculated by adding three standard deviation units to the mean absorbance of five complement fixation antibody-negative (titers <8) specimens. A positive IgM result was considered diagnostic only if a simultaneous high level of IgG antibody was found.

Viral antibodies for coxsackievirus B4 were determined by indirect EIA methods.[14] Instead of endpoint titer, relative EIA-unit scaling was used for expression of quantitative antibody activity.[14]

Definitions

A case of acute bacterial meningitis was defined as a patient who had at least one of the following: a positive bacterial culture of CSF, positive bacterial antigen detection in CSF, or positive blood culture with CSF pleocytosis. A diagnosis of definitive viral CNS infection was based either on a positive viral culture of the CSF or on typical clinical presentation of measles or rabies encephalitis, or paralytic poliomyelitis. Probable viral diagnosis was based on CSF findings compatible with meningitis together with at least a twofold increase in specific IgG antibody titer or a positive IgM result with simultaneously elevated IgG antibody levels.

Statistical Analysis

The means of observations were compared using Student's t-test ($P < 0.05$ considered significant).

RESULTS

Clinical Diagnosis

The following diagnoses, based on clinical and laboratory data available at the time of hospital discharge, were set by the attending physicians: meningitis (n = 71), encephalitis (n = 21), brain abscess (n = 3), and poliomyelitis (n = 1). Two patients had sepsis as discharge diagnosis, one of them had sepsis neonatorum with CSF pleocytosis, and the other one had fatal meningococcemia with CSF pleocytosis. In patient records, the discharge diagnosis of another two patients was given as febrile convulsions with CSF pleocytosis. In three cases the discharge diagnosis given by the clinician could not be retrieved.

Bacterial Etiology

Evidence of etiology was obtained in 60 (58%) of the 103 Filipino patients with a CNS infection included in this study (Table 1). There were 19 cases of acute bacterial meningitis, of whom the diagnosis was based on positive CSF culture in 9 cases, on CSF pleocytosis with positive blood culture in 6 cases, on antigen detection with positive Gram stain in 2 (both *S. pneumoniae*), and on positive antigen detection alone in 2 (1 *S. pneumoniae*, 1 *H. influenzae* type b). Computerized tomography of the head was performed on 32 patients; 3 were diagnosed as having a brain abscess, without evidence of specific etiology.

The diagnosis of tuberculous meningitis was based on histologic autopsy findings in all four cases (4%). There was also one more autopsy-proven tuberculous meningitis case who was classified as bacterial meningitis for the analysis of clinical correlates, based on a positive blood culture (*H. influenzae* type b and beta-hemolytic streptococcus) on admission. She died after 5 weeks of treatment in the hospital. Culture methods for mycobacteria were not available at the time of the study. The diagnosis of the only case of cryptococcal meningitis was based on a positive CSF culture.

Table 1. Etiology and age distribution of 103 Filipino patients with CNS infection.

Age	*0-2mo*	*3-11mo*	*12-23mo*	*2-4y*	*5-15y*	*>16y*	*all*
Bacteria	4	11	3		1		19
Haemophilus influenzae b*		4	1				5
Neisseria meningitidis		2			1		3
Streptococcus pneumoniae	3	3	1				7
Escherichia coli	1						1
Flavobacterium meningosepticum		1	1				2
Salmonella Typhi		1					1
Mycobacterium tuberculosis			1	1		2	4
Brain abscess				1		2	3
Viruses	1	6	12	8	7	4	38
Cryptococcus						1	1
Etiology not known	6	7	5	6	14	5	43
All	11	24	21	16	22	14	108**

* One case had a mixed infection with group A beta hemolytic streptococcus.
** Exceeds the number of patients because 5 patients had evidence of both bacterial and viral etiology.

Table 2. Age distribution of patients with viral CNS infection

Age	*0-2mo*	*3-11mo*	*12-23mo*	*2-4y*	*5-15y*	*>16y*	*All*
Definitive diagnosis	1	2	2	5	2	1	13
Virus isolated from CSF							
Coxsackie A9			1				1
Echo 9	1						1
Enterovirus, not spesified				1			1
Mumps					1¶		1
Typical clinical presentation							
Measles encephalitis		1	1	4			6
Poliomyelitis	1						1
Rabies	1	1	2				
Probable diagnosis‡	4	10	3	5	3	25	
Adeno			2				2
Coxsackie B		2*	3*	2	4	1	12
Coxsackie B and Adeno			2				2
Coxsackie B and Herpes Simplex				1			1
Coxsackie B and Measles			1*				1
Coxsackie B and Polio		2*					2
Herpes simplex					1		1
Measles						1*	1
Mumps			1				1
Polio			1			1	2
All	1	6	12	8	7	4	38

¶This patient had also diagnostic serology for mumps and coxsackie B.
‡ Diagnostic antibody finding.
* A patient with a mixed (viral and bacterial) infection, one for each asterisk.

Viral Etiology

Viral etiology alone was detected in 33 patients (32%), an additional 5 patients had diagnostic viral serology with a concomitant finding from another etiologic group (Table 2). Definitive viral diagnosis was based either on a positive viral culture of the CSF (n = 4) or on typical clinical presentation of measles encephalitis (n = 6), rabies (n = 2, one autopsy proven), or paralytic poliomyelitis (n = 1). A probable viral diagnosis was based on serology in 20 cases. The additional five cases with concomitant viral and bacterial diagnosis had either an acute bacterial meningitis (one coxsackievirus B with *S. pneumoniae*, one coxsackievirus B and polio with *Salmonella typhi*, one coxsackievirus B and measles with *Flavobacterium meningosepticum*), tuberculous meningitis (coxsackievirus B), or brain abscess (measles).

C-Reactive Protein in Differential Diagnosis

In 18 of 19 bacterial meningitis cases, serum CRP levels were determined on admission. C-reactive protein concentrations were elevated in all of these patients (mean 207 ± 111 mg/L). In 17 (94%) of 18 bacterial meningitis cases, the CRP concentration was over 50 mg/L; in 14 of them, over 100 mg/L (Figure 1). The lowest CRP concentration on admission was 43 mg/L. This patient had fatal meningococcemia, and her symptoms had lasted only 12 hours before admission. Eight of the 18 patients with bacterial meningitis and CRP determined had received antibiotics prior to admission; their mean CRP concentration (196 ± 91 mg/L) was similar to patients without preadmission antibiotic treatment (204 ± 131 mg/L).

There were three cases of brain abscess confirmed by CT; two of these had CRP levels of 11 mg/L and 135 mg/L on admission, respectively, and in one case CRP was not determined on admission.

Serum CRP was determined on admission in 30 of the 33 cases with viral CNS infection. Five patients with mixed bacterial and viral etiology were included only in the group of bacterial etiology for the analysis of CRP and other laboratory tests. The mean CRP concentration of the patients with a viral infection (39 ± 34 mg/L)

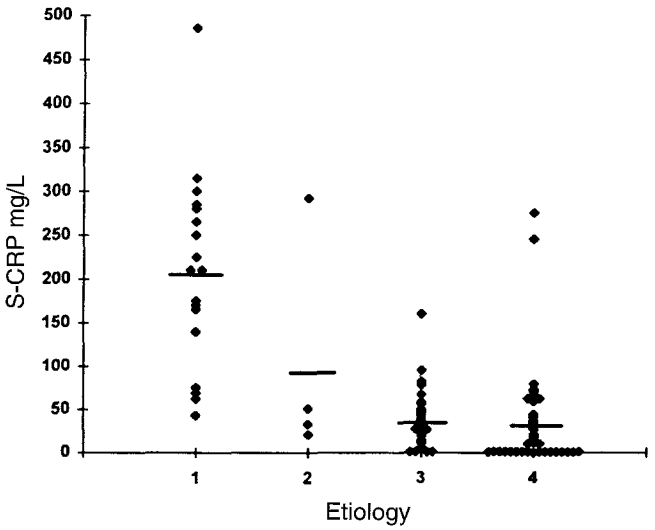

Figure 1. Serum CRP concentration in patients with CNS infection of different etiology. Etiologic grouping indicated: 1. Bacterial, 2. Tuberculous, 3. Viral, 4. Unknown etiology.

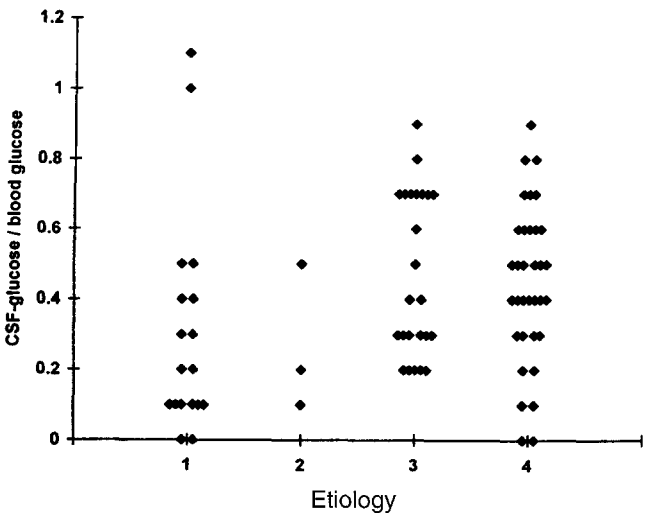

Figure 2. The ratio of CSF glucose to blood glucose in patients with CNS infection of different etiology. Etiologic grouping indicated: 1. Bacterial, 2. Tuberculous, 3. Viral, 4. Unknown etiology.

was significantly lower than CRP of the patients with a bacterial infection ($P < 0.001$) but ranged widely from <10 mg/L to 160 mg/L (see Figure 1). In nine cases (30%) the CRP value on admission was below 20 mg/L, and in nine cases (30%) CRP was at least 50 mg/L. Whether the specific viral diagnosis was obtained by viral isolation, clinical presentation (measles, rabies, poliomyelitis), or serology, the CRP values seemed to be similar in different groups; however, the groups were small. Within the patient group where the etiology could not be determined, the CRP values varied widely (mean = 35 ± SD59 mg/L) and in 10 cases (23%) CRP was clearly elevated (>50 mg/L).

Other Laboratory Findings

Cerebrospinal fluid sample was taken on admission in 18 of 19 cases with bacterial meningitis and in 26 of 33 cases with viral etiology. The number of polymorphonuclear (PMN) leukocytes in the CSF was not significantly higher in patients with bacterial infection (mean = 389 $\times 10^6$/L ± 1052 $\times 10^6$/L) compared to those with viral etiology (mean = 77 $\times 10^6$/L ± 298 $\times 10^6$/L). In nine cases of bacterial meningitis (50%), the number of PMN leukocytes in CSF was below 10 $\times 10^6$/L. The mean number of PMN leukocytes in CSF was 17 $\times 10^6$/L ± 13 $\times 10^6$/L in patients with tuberculous meningitis, 422 $\times 10^6$/L ± 2084 $\times 10^6$/L) in patients with unknown etiology, and was determined in only one case with a brain abscess (1224 $\times 10^6$/L). The ratio of CSF glucose to blood glucose was decreased in bacterial infections, being 0.4 or lower in 14 cases (Figure 2). In the viral group, 13 patients (54% of the viral cases with CSF:blood glucose ratio determined) had a CSF:blood glucose ratio 0.4 or lower and, thus, could not be differentiated from patients with bacterial etiology. Cerebrospinal fluid protein level was elevated (>450 mg/L) in 15 cases (83%) with bacterial infection (mean = 1551 ± 1309 mg/L) and in 13 cases in the viral group (52% of viral cases with CSF protein determined; mean = 1545 ± 3297 mg/L). The difference in CSF protein concentration was not significant between these two groups.

Sensitivity and Specificity

The sensitivity and specificity of serum CRP value of 50 mg/L or higher to detect acute bacterial meningitis was 94% and 65%, respectively. The positive predictive value was 57%, and negative predictive value, 96%. For acute bacterial meningitis, the ratio of CSF glucose to blood glucose with a limit of 0.4 or lower had sensitivity, specificity, positive, and negative predictive values of 78%, 41%, 42%, and 76%, respectively.

DISCUSSION

This study included 103 Filipino patients with a CNS infection admitted to a hospital that functions as both a local and a referral hospital. Using a wide range of diagnostic tools for the etiology of CNS infection, the authors found elevated CRP values in all cases of bacterial meningitis, with a mean significantly higher than that in viral CNS infections. However, the presence of considerable overlap between these groups, and the varying CRP concentrations in patients with tuberculous meningitis as well as brain abscess reduced the predictive value of CRP in choosing the optimal treatment for CNS infections.

The goal was to study the usefulness of serum CRP in an unselected patient population and to include not only clear-cut bacterial and viral meningitis cases but also brain abscess, tuberculous meningitis, encephalitis, and partially treated bacterial meningitis cases as they appear in regular clinical practice. In this study, a head CT, uncommon for clinical practice in a developing country, was performed in one third of the patients. Of the bacterial meningitis cases, as many as one fourth had negative bacterial cultures but were diagnosed by antigen detection, suggesting a good diagnostic potential of these methods. Antigen detection tests in CSF for *H. influenzae* b, *S. pneumoniae*, and *N. meningitidis* have been shown to be highly specific, with sensitivities ranging from 50 to 95%.[15] Preadmission antibiotic therapy was as common in culture-positive as in culture-negative bacterial meningitis cases.

There have been few reports on the viral etiology of CNS infections in developing countries.[4] In the present study specific viral etiology was detected in one third of patients. In most cases of viral infections, the specific diagnosis was based on positive serology that indicated a recent infection but was not definite proof for CNS involvement. As it is known that many viruses can be

cultured from stool and throat swab samples in asymptomatic patients in unhygienic conditions, the authors did not include these data in the final analysis. In two thirds of cases with viral etiology, the infection was caused by enteroviruses (coxsackie, polio, echo). Every fifth viral CNS infection was caused by measles, a number that has since probably been declining owing to increasing vaccination coverage. Of 60 cases with specific diagnosis, 10 patients presented with proven dual etiology (bacterial-viral in 5 cases, viral-viral in 5 cases). This probably reflects the strong infectious pressure from the environment in these age groups under these circumstances. Diagnostic methods did not cover Japanese B encephalitis, rickettsiae, or leptospirosis, which could have been the cause in some of the cases without specific etiology.

Serum CRP was elevated on admission in all patients with bacterial meningitis. In this group, CRP was below 50 mg/L in only one case; she had had symptoms for only 12 hours before admission. Previous reports also have described cases in the early phase of bacterial meningitis with low CRP concentration.[9,16] Preadmission antibiotic treatment did not affect the CRP values in patients with bacterial meningitis.

Patients with viral etiology had a significantly lower mean CRP concentration than patients with bacterial meningitis. However, in this study, there was more overlap with the bacterial group than in previous reports.[7,9] In developing countries patients may seek medical care later and with more severe symptoms than in developed countries. There could have been more mixed infections (e.g., culture methods for tuberculosis were not available) in this patient population. It also is known that certain viral infections, such as measles and adenovirus can cause CRP elevation.[17,18]

C-reactive protein values of the small number of patients with brain abscess or tuberculous meningitis varied widely in this study. In another study, CRP was found to be moderately elevated in patients with miliary (median 105 mg/L) and non-miliary (40 mg/L) tuberculous meningitis.[8] Owing to the high prevalence of tuberculosis in developing countries, these moderately elevated CRP values may confound the use of CRP in differentiating the viral and bacterial etiology of CNS infections and, thus, complicate the decision for the appropriate treatment modality. The wide range of CRP values in patients with unknown etiology together with other clinical information, suggests that patients belonging to all etiologic groups fall into this category.

The ratio of CSF glucose to blood glucose was decreased in patients with bacterial meningitis. Yet there was considerable overlap between patients with bacterial or viral infection, thereby complicating clinical decision making. Neither CSF leukocyte count nor CSF protein concentration could significantly differentiate these two etiologic groups.

In this study, it was demonstrated that normal CRP levels (below 10 mg/mL) exclude the possibility of acute bacterial meningitis, and these patients do not need antimicrobial therapy. However, elevated CRP values can be caused not only by bacterial meningitis but also by tuberculous meningitis, brain abscess, and viral CNS infection, thereby complicating the choice of treatment in these patients.

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