Value of C reactive protein measurement in tuberculous, bacterial, and viral meningitis

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SUMMARY The value of C reactive protein measurement in the differential diagnosis of meningitis was assessed in a population where tuberculous meningitis is prevalent. C reactive protein was measured serially with a sensitive radioimmunoassay in sera from 31 children with bacterial meningitis, 15 with tuberculous meningitis (6 with miliary tuberculosis), and 28 with viral meningitis. Concentrations of C reactive protein in patients with tuberculous meningitis lay between those of patients with bacterial and viral meningitis—a finding which detracts from the virtually absolute discrimination C reactive protein measurement allows between bacterial and viral meningitis. In all but two of the patients with tuberculous meningitis, C reactive protein concentrations fell rapidly after treatment began and became normal after 10 days. This fall did not, however, exclude the development of hydrocephalus as a complication. Measurement of C reactive protein remains a useful additional parameter in the diagnosis and management of the various types of meningitis.

C reactive protein is the classic acute phase reactant—its concentration in serum rises up to a thousandfold in response to most forms of tissue damage, inflammation, and infection. As increased hepatic production of C reactive protein is a rapid and sensitive response to most forms of microbial infection, the value of its measurement in the diagnosis and management of various infective conditions has been established. Attention was recently drawn to the value of serum C reactive protein measurement in differentiating bacterial and viral meningitis in a developed western society. The present study investigates the value of serial C reactive protein measurements in the diagnosis and management of meningitis in a developing society in which tuberculous meningitis is prevalent.

Patients and methods

Seventy four children (aged from 3 months to 15 years) in whom a definite diagnosis of bacterial, tuberculous, or viral meningitis was made at this hospital between June 1982 and April 1983 were studied. Fifty five of these patients were of mixed race (Cape Coloured), 7 were white, and 12 were black. Serial serum samples, taken for other diagnostic reasons at the time of diagnosis and at intervals not exceeding four days after treatment began, were analysed retrospectively.

Bacterial meningitis, diagnosed in 31 patients on the basis of cerebrospinal fluid cellular and biochemical findings, was confirmed by positive blood or cerebrospinal fluid culture, or both. The aetiologic agent in 22 patients was Neisseria meningitidis, in 6 Haemophilus influenzae, and in three Streptococcus pneumoniae.

Two groups of patients with tuberculous meningitis were studied. The first group comprised 6 patients with miliary tuberculosis and meningeal involvement (miliary tuberculous meningitis) and the second group of 9 patients had tuberculous meningitis without clinical evidence of miliary tuberculosis (non-miliary tuberculous meningitis). The diagnosis of tuberculous meningitis was made on the basis of classic cerebrospinal fluid cellular response and biochemical analysis, including adenosine deaminase measurements. Mycobacterium tuberculosis was identified by direct immunofluorescent staining or culture in 7 of these patients.

Patients with viral meningitis were included in this study only if compatible cerebrospinal fluid cellular response and biochemical analysis was accompanied by spontaneous recovery without antimicrobial treatment. Cerebrospinal fluid and other appropriate specimens cultured for bacteria and M tuberculosis were negative in all cases.

All patients with tuberculous meningitis were treated with a four drug regimen comprising iso-
niazid, rifampicin, pyrazinamide, and ethionamide. Prednisone (2 mg/kg) was given to five of the 6 patients with miliary tuberculosis and to 7 of the 9 children with non-miliary tuberculous meningitis. All patients with tuberculous meningitis had regular, computed tomography for the early identification of hydrocephalus.

Serum samples were stored at −20°C after separation. Samples were thawed and run in batches to determine the concentration of C reactive protein using a new, rapid radioimmunoassay which allows a single operator to achieve a manual throughput of some 50 samples per hour.\(^8\) This assay uses a magnetisable cellulose solid phase and determinations have intra- and interassay coefficients of variation of less than 10%.

Statistical analysis was done using the \(\chi^2\) test (4\times4 contingency table) and statistical significance of differences between groups was sought by means of Wilcoxon rank sum tests.

Results

The C reactive protein concentrations of patients with bacterial, miliary and non-miliary tuberculous, and viral meningitis are illustrated in Fig. 1. Patients with bacterial meningitis had C reactive protein concentrations ranging from 41 to 400 mg/l with a median value of 260 mg/l, which was significantly higher (P<0.001) than patients with viral meningitis who had a median value of 10 mg/l. Concentrations in meningococcal meningitis did not differ significantly from those in other forms of bacterial meningitis (data not shown). The patient with viral meningitis who had the highest C reactive protein concentration (45 mg/l) also had parotitis complicated by suspected pancreatitis with a plasma amylase value of 2000 Street-Close units.

C reactive protein concentrations in patients with both miliary (median 105 mg/l) and non-miliary tuberculous meningitis (median 40 mg/l) were intermediate—lying between those of patients with bacterial and viral meningitis. Patients with miliary tuberculous meningitis, however, had significantly higher concentrations than those with non-miliary tuberculous meningitis (P<0.01). By establishing the C reactive protein ranges 0 to 20 mg/l for viral meningitis, 20 to 60 mg/l for non-miliary tuberculous meningitis, 60 to 180 mg/l for miliary tuberculous meningitis, and 181 mg/l and above for bacterial meningitis, we were able to show that C reactive protein concentrations were significantly dependent (P<0.001) on the disease grouping.

Fig. 2 shows serial C reactive protein concentrations in three of the 6 children with miliary tuberculous meningitis after beginning antituberculous treatment. Five of the 6 patients with miliary

![Fig. 1 C reactive protein concentrations in bacterial meningitis, miliary tuberculous meningitis, non-miliary tuberculous meningitis, and viral meningitis.](image)

![Fig. 2 C reactive protein concentrations in miliary tuberculous meningitis after antituberculous treatment. Cases 1 and 2 received steroids and developed hydrocephalus; case 3 did not receive steroids and was clinically well at 12 days.](image)
tuberculosis received steroids; the sixth child (case 3) recovered and no evidence of hydrocephalus was found at 12 days. His C reactive protein concentration fell rapidly, becoming normal 8 days after treatment was started. Two of the patients treated with steroids died soon after admission to hospital. Only one of the remaining patients did not show a rapid decline in C reactive protein concentrations after treatment; this child (case 1) developed hydrocephalus and died 10 days later. Although the C reactive protein concentrations declined rapidly in the remaining two patients, one (case 2) developed hydrocephalus 8 days after treatment was started.

Fig. 3 shows the C reactive protein concentrations in three patients with non-miliary tuberculous meningitis in response to treatment. Two of the 9 patients with non-miliary tuberculous meningitis did not receive steroids and showed rapidly declining C reactive protein concentrations after treatment started—one (case 6) developed hydrocephalus. One of the 7 patients receiving steroids died soon after hospital admission and 6 showed declining C reactive protein concentrations, which became normal 10 days after treatment started (for example, case 4). Two of these 6 patients developed hydrocephalus. One patient (case 5) showed a continuing acute phase response despite treatment (with C reactive protein concentrations fluctuating around 25 mg/l) and developed hydrocephalus 10 days after hospital admission.

Discussion

The aetiological diagnosis of meningitis remains a problem in clinical practice as cerebrospinal fluid biochemical analysis and cellular responses often overlap. This becomes even more difficult in a population where tuberculous meningitis is prevalent, as M tuberculosis is not always easily and reliably identifiable in cerebrospinal fluid by established techniques. Because of the long term therapeutic and prognostic implications of tuberculous meningitis, additional diagnostic parameters would be of great importance.

Our data confirm that C reactive protein determinations in serum differentiate reliably between bacterial and viral meningitis, even though the concentrations in our patients with viral meningitis were higher than those published in other studies. This could be due to the more severe clinical course of viral infections (for example, measles) in underprivileged peoples or to undiagnosed concomitant, minor bacterial infections. The patient with the highest C reactive protein concentration in the viral group had parotitis with suspected pancreatitis which could explain his relatively high concentrations.

C reactive protein concentrations in tuberculous meningitis are intermediate, lying between those of bacterial and viral meningitis. Although the concentrations in miliary tuberculosis are significantly lower than in bacterial meningitis (P<0.01), however, the overlap detracts from the clinical usefulness. C reactive protein measurements differ significantly (P<0.01) between viral and non-miliary tuberculous meningitis. By establishing a range for viral meningitis from 0 to 20 mg/l and from 21 to 60 mg/l for non-miliary tuberculous meningitis we have shown that the C reactive protein concentration is significantly (P<0.001) dependent on the disease grouping.

The rapid decline in concentrations after treatment in most patients with tuberculous meningitis is of diagnostic value. This decline does not, however, exclude hydrocephalus as a complication. In the limited number of patients studied, treatment with steroids did not seem to affect the decline in concentrations of C reactive protein (Figs. 2 and 3). We conclude that the measurement of C reactive protein in a population where tuberculous meningitis is prevalent remains useful in the diagnosis of meningitis, despite the fact that concentrations in tuberculous meningitis are intermediate, lying between those found in viral and bacterial meningitis. In a developed society, where tuberculous meningitis is rare, a C reactive protein concentration between 21 to 60 mg/l in a patient with meningitis...
should caution the clinician to consider non-miliary tuberculous meningitis.

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