Changes in Serum C-Reactive Protein During Complicated and Uncomplicated Measles Virus Infections

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Serum C-reactive protein levels become elevated coincident with the onset of the rash in patients with measles. Serum C-reactive protein elevations are prolonged in measles complicated by pneumonia and may show a second elevation in measles complicated by encephalitis.

Fever is a manifestation of many diseases—viral, bacterial, and immune mediated. It has recently been shown that endogenous pyrogen, the substance indirectly responsible for fever production, is a product of monocytes (8). This monokine has many functional properties and has recently been given the encompassing name interleukin-1 (IL-1) (18). Macrophages can be induced to produce IL-1 by a number of stimuli, including bacterial endotoxins, T-cell lymphokines, and particle ingestion (2, 23). In addition to being responsible for the generation of fever and T-lymphocyte proliferation, IL-1 also induces increased hepatic synthesis of a number of serum proteins. The prototype of these “acute-phase reactants” is C-reactive protein (CRP) (1, 17, 21).

Although fever is a common manifestation of viral infections, elevated CRP occurs infrequently and has often been used to distinguish bacterial from viral infections (15, 20). Since the rash of measles may be a manifestation of the cellular immune response to this virus (7, 12), it seemed likely that CRP might be increased at least transiently during viral infection. The purpose of this study was to determine whether the onset of the cellular immune response in measles is accompanied by sufficient systemic production of IL-1 to increase hepatic synthesis of CRP, resulting in increased levels of CRP in serum. Levels of CRP were also measured in children with measles virus infections complicated by pneumonia (usually bacterial) or encephalitis.

A total of 168 patients from several sources in Lima, Peru, were studied. For the most part, patients with uncomplicated measles (n = 65) were referred from the emergency room at the hospital of Universidad Peruana Cayetano Heredia or from a local community health center at Canto Grande, approximately 10 km from the university. Patients with measles pneumonia (n = 60) and control patients with other infectious diseases (n = 23) were seen on the infectious disease wards at Hospital del Niño. Patients with postinfectious encephalomyelitis (n = 19), referred to us by local neurologists and pediatricians, were seen at several hospitals in Lima. Control patients with other neurological diseases (n = 5) were seen in the pediatric neurology clinic at the university or on the pediatric neurology ward at Hospital del Niño. Some patients were studied several times during the course of their disease. Studies were approved by the committees for Clinical Investigation at The Johns Hopkins University School of Medicine, Baltimore, Md., and at the Universidad Peruana Cayetano Heredia.

Blood was collected in sterile, disposable syringes and transferred to tubes containing preservative-free heparin (20 U/ml of blood). Blood was transported within 1 h to our laboratories, where plasma was separated from the cells used for assays of cell-mediated immunity (R. L. Hirsch, D. E. Griffin, R. T. Johnson, S. J. Cobb, I. Lindo de Soriano, S. Roedenbeck, and A. Vaisberg, submitted for publication). Plasma was frozen at −20°C until thawed for assay. CRP was measured by radial immunodiffusion (14). Standard sera, prepared immunodiffusion plates (LC-partigen CRP kit), and antiserum to CRP were purchased from Calbiochem, La Jolla, Calif. The level of sensitivity of the assay was 0.6 mg/dl. For purposes of calculating averages, patients with CRP levels below this amount were scored at 0. Plasma obtained from a patient at The Johns Hopkins Hospital was assayed for...
TABLE 1. CRP levels in patients with measles and in control patients with other diseases

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. of samples</th>
<th>Mean day of disease</th>
<th>CRP ± SEM (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Uncomplicated</td>
<td>73</td>
<td>6.7</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>62</td>
<td>6.7</td>
<td>4.2 ± 0.5</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>35</td>
<td>19.4</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>4</td>
<td>13.7</td>
<td>5.9 ± 2</td>
</tr>
<tr>
<td>Other viral infections</td>
<td>19</td>
<td>10.9</td>
<td>0.3 ± 0.3</td>
</tr>
<tr>
<td>Other neurological diseases</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Number of patients with other viral infections: polio, 14; mumps, 2; viral encephalitis, 2; varicella, 1.
* Number of patients with other neurological diseases: Guillain-Barre syndrome, 3; ataxia after varicella, 1; epilepsy, 1.

CRP levels before and after being frozen. No change in the level of CRP was detected.

A total of 73 plasma samples from 65 patients with uncomplicated measles ranging from 1 day before (Koplik spots) to 30 days after the onset of the exanthem (mean, 6.7 days), 62 plasma samples from 60 patients with measles complicated by pneumonia (days 1 to 26, mean, 6.7 days), and 35 plasma samples from 19 patients with measles complicated by encephalitis (days 3 to 90, mean, 19.4 days) were assayed for CRP. Positive controls were provided by four patients with typhoid fever. Negative controls were provided by 5 patients with other neurological diseases and 19 patients with viral infections other than measles (14 with polio, 2 with mumps, 2 with viral encephalitis, and 1 with varicella). All groups of patients with measles had elevated CRP levels compared with the negative controls (Table 1).

CRP levels were analyzed in the uncomplicated cases by the stage of infection. CRP levels were only slightly above normal (4) before the rash, were most elevated at the onset of the rash (day 0 to 1), and gradually fell thereafter (Fig. 1). In patients with pneumonia, CRP levels were higher and remained elevated for longer periods of time. The onset of the rash in measles, as well as recovery from infection, probably depends on the cellular immune response to the virus, since individuals with T-cell deficiencies tend to develop disseminated infection in the absence of a rash (7, 13). The fact that CRP levels were essentially normal before the appearance of the rash but clearly elevated at the time of the rash and for several days thereafter is consistent with the hypothesis that the rash is a manifestation of virus-specific cell-mediated immunity (12). A similar time course of CRP elevation has been observed during another viral exanthem, rubella (22). In vitro parameters of cellular immunity to measles virus are also positive at this time during infection (10, 25; Hirsch et al., submitted for publication). This finding does not correlate, however, with the onset of fever, which is typically present during the prodromal phase as well as with the rash. Since macrophages are capable of making more than one species of IL-1 in response to infection (19), it is possible that these species of IL-1 differ in their relative efficiency in producing fever or in stimulating hepatic synthesis of acute-phase reactants.

CRP levels were also studied in patients with measles complicated by encephalitis. CRP levels are usually normal in patients with viral meningitis and encephalitis (9, 20, 24; Table 1), although the mononuclear inflammatory reaction to most viral infections of the central nervous system (CNS) is an immunologically mediated response (3, 5, 16). However, in measles encephalitis it is unclear whether the CNS disease is caused by direct viral invasion of the brain or by an abnormal immune response to CNS antigens (11, 12). Children who develop encephalitis typically have a biphasic disease. Usually the fever is abating and the rash is fading when the CNS symptoms, accompanied by a second episode of fever, occur. In experimental allergic encephalo-

FIG. 1. Averaged CRP levels at various times after the onset of rash in the serum of patients with uncomplicated measles or measles complicated by pneumonia. Uncomplicated measles patients had no evidence of superimposed bacterial infection, whereas those with pneumonia often did. Error bars indicate the standard error of the mean for each group. Number of uncomplicated patients studied: before rash, 6; days 0 to 1, 24; days 2 to 3, 12; days 4 to 8, 13; and days ≥9, 18. Number of pneumonia patients studied: days 1 to 3, 15; days 4 to 5, 16; days 6 to 8, 17; and days ≥9, 14.
myelitis, an immune-mediated disease of the CNS, elevated levels of CRP are found in the sera of rabbits coincident with the onset of the disease (5). To determine whether there is any evidence for a second episode of cell-mediated immune response, data from encephalitis patients were analyzed by time of onset of encephalitis as well as by the onset of rash, since encephalitis occurred at a variable time relative to the rash (day −9 to 20) in these patients (Fig. 2). Elevations of CRP were greatest soon after the onset of encephalitis and after the onset of the rash. Too few early samples after encephalitis were available to determine whether this reflected two separated CRP peaks or merely the fact that most of the children developed encephalitis 4 to 5 days after the appearance of the rash, when CRP levels are normally still elevated.

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FIG. 2. CRP values for individual patients with post-measles encephalomyelitis. Values are plotted according to the day after the onset of encephalitis symptoms. Numbers above data points are days after onset of rash.

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