

C-Reactive Protein Levels in Children with Primary Herpetic Gingivostomatitis

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ABSTRACT: **Background:** C-reactive protein (CRP) is often used to distinguish bacterial from viral infections. However, the CRP level does have implications, which depend on the clinical scenario and are still under research.

Objectives: To evaluate the distribution of CRP levels in children with primary herpetic gingivostomatitis.

Methods: The electronic database of a tertiary pediatric medical center was searched for all inpatients with a diagnosis of primary herpetic gingivostomatitis without bacterial co-infection. Background and clinical information was collected and CRP levels were analyzed.

Results: The study group consisted of 66 patients aged 8 months to 7.1 years who met the study criteria. The average CRP was 7.4 mg/dl (normal < 0.5 mg/dl). More than a third of the patients had a level higher than 7 mg/dl.

Conclusions: High values of CRP are prevalent in patients with primary herpetic gingivostomatitis, similar to adenoviral infections and some bacterial infections.

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KEY WORDS: C-reactive protein (CRP), herpes simplex virus, infection, inflammation, primary herpetic gingivostomatitis

C-reactive protein (CRP) is a host-mediated inflammatory marker. Measurements of CRP are frequently used to help clinicians differentiate viral from bacterial infections, owing to the statistically higher levels of CRP observed during bacterial infections, as shown by us and others [1-4]. Different cutoffs have been proposed, with the sensitivity and specificity varying accordingly [1]. However, adenoviral infections have been shown to be associated with high levels of CRP [5]. This phenomenon, if present in other viral infections, can mislead clinicians to overuse of antibiotics.

Primary herpetic gingivostomatitis, an initial infection with herpes simplex virus, typically occurs in children aged between 6 months and 5 years. The diagnosis is usually straightforward, based on the characteristic clinical manifestations of erythematous gingiva, mucosal hemorrhages, and clusters of small vesicles erupting throughout the mouth. There is often involvement of the mucocutaneous margin and perioral skin

[6]. The oral symptoms are generally accompanied by high fever, lymphadenopathy, and difficulty eating and drinking. Symptoms regress within 2 weeks without specific therapy. The most prevalent complication is dehydration. Bacterial co-infections or secondary infections are uncommon, although bacteremia may occur [6].

Our experience in the pediatrics department at a major children's hospital has suggested that primary herpetic gingivostomatitis, like adenoviral infection, may induce high bacterial infection-like levels of CRP. The purpose of the present study was to evaluate CRP levels in this infection with the purpose of helping clinicians make more knowledgeable empiric treatment decisions in doubtful cases.

PATIENTS AND METHODS

The computerized medical records of a tertiary, university-affiliated, pediatric medical center were searched for patients hospitalized for primary herpetic gingivostomatitis. Data were available for the period between February 2004 and May 2011. For purposes of the study, herpetic gingivostomatitis was defined as clinical gingivostomatitis with virologic culture evidence of oral herpes simplex virus type 1 or 2.

Patients missing blood culture or CRP data were not included, nor were patients with a positive blood culture or any other evidence of a bacterial infection. Background information was collected and CRP levels were recorded and analyzed. Findings were additionally analyzed separately for patients treated with antibiotics during hospitalization versus those who were not. The study was approved by the Institutional Review Board.

RESULTS

The 66 patients who met the inclusion criteria comprised 29 boys and 37 girls, ranging in age from 8 months to 7.1 years. The range of hospital stay was 1 to 7 days. Forty-eight children were not treated with antibiotics and 18 were empirically treated with antibiotics at some point during the hospitalization.

The background and CRP results for the two groups are shown in Table 1. The mean CRP level for the whole cohort was 7.4 mg/dl (normal < 0.5 mg/dl), the standard deviation

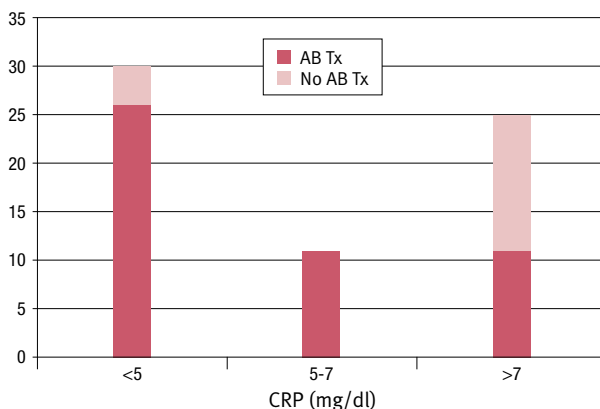
Table 1. Background characteristics and CRP levels in patients with primary herpetic gingivostomatitis treated/not treated with antibiotics

Group	Age, mean (range)	M:F ratio	LOS, average (range)	CRP (mg/dl), average (range)	CRP (mg/dl), median	CRP > 5 mg/dl, % patients
No antibiotic treatment (n=48)	2.4 yr (8 mo to 7.1 yr)	0.92	3.6 days (1-11)	5.5 (0.5-41.6)	4.1	46%
Antibiotic treatment (n=18)	2.3 yr (11 mo to 5.5 yr)	1	4.7 days (3-7)*	12.4* (0.7-22.4)	9.8	78%

*P < 0.05

CRP = C-reactive protein, LO = length of hospital stay

Figure 1. Distribution of CRP values in 66 children with primary herpetic gingivostomatitis and no evidence of a bacterial co-infection or secondary infection



AB Tx = antibiotic treatment

was 7 and the median 5.7 mg/dl. The distribution of CRP levels is presented in Figure 1. CRP levels were above normal in all patients, higher than 5 mg/dl, 7 mg/dl and 10 mg/dl in 55%, 37% and 24% of the cohort, respectively.

Children who were treated with antibiotics tended to have higher CRP levels than those who were not, and they had a significantly longer average hospital length of stay ($P < 0.05$, Table 1).

No correlation was found between the CRP level and the age of the child, the maximum temperature reported during the illness (mean 39.6°C), the day of illness in which CRP was examined (mean 5), or the white blood cell count (mean 12,200/ μ l).

DISCUSSION

This study demonstrates that elevated levels of CRP are found in most hospitalized children with primary herpetic gingivostomatitis, without a bacterial co-infection or secondary infection.

Although CRP is usually a valuable tool for distinguishing viral from bacterial infections, its application is still controversial [7-9]. A major problem is the overlap of values between these two conditions. For example, a cutoff of 7 mg/dl in febrile children without localizing signs has a specificity of 90% in identifying serious bacterial infection but a sensitivity of only 79% [10]. Although viral infections are usually associated with relatively low levels of CRP, exceptionally high levels have been reported in patients with adenovirus infection, with 24% having levels above 10 mg/dl [2,11]. Similarly, in our cohort of patients with primary herpetic gingivostomatitis, more than one-third had CRP values higher than 7 mg/dl and almost one-fourth had values higher than 10 mg/dl. Therefore, like for adenovirus, CRP levels appear to be generally higher in primary herpetic gingivostomatitis than in most other viral diseases.

The mechanisms underlying the induction of CRP synthesis in different circumstances are still being researched. Cytokines such as interleukin-6 and tumor necrosis factor-alpha have been shown to be involved [12-16], but their connection to specific characteristics of the offending microorganism is unknown. It is possible that adenovirus and herpes simplex virus share specific phenotypes with bacteria, leading to an inflammatory response similar to that for bacterial infection.

Thus, the CRP level may have diagnostic benefit when the data are insufficient to determine whether the origin of an infection is viral or bacterial, as in patients with fever without localizing signs or patients with pneumonia. However, when the clinical signs and symptoms are characteristic of a viral disease, CRP measurement, like any unnecessary laboratory test, may lead to unwarranted treatment with potential adverse effects and risks. In this study, children who were treated with antibiotics had on average higher CRP levels. These children were also hospitalized for longer periods.

The retrospective nature of this work precludes a definitive conclusion regarding the contribution of higher levels of CRP to the decision to initiate antibiotic treatment, but it is possible that the high CRP level, despite the clinical diagnosis of herpetic gingivostomatitis, prompted the antibiotic use. It is also possible that the children with higher CRP levels also shared other characteristics, such as a poorer general condition, which would contribute to the differences observed between the groups. Other causes, such as bacterial infections that were not recorded in the patient files, also cannot be ruled out retrospectively.

To the best of our knowledge, this work is the first to systematically evaluate CRP values in children with confirmed primary herpetic gingivostomatitis. However, the distribution of CRP described here may not represent the full range of patients with primary herpetic gingivostomatitis. Due to the strict inclusion criteria, i.e., studying only patients who were admitted to the hospital and for whom blood cultures were examined, our data are probably biased towards the more severely ill children.

Prospective studies are needed to make more efficient use of inflammatory markers. In the meantime, we recommend that clinicians consider the possibility of intrinsic high CRP levels when treating children with primary herpetic gingivostomatitis in whom there is no other evidence of a bacterial infection, and consider withholding antibiotic use in such cases.

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