Cytokine Levels in Gingival Crevicular Fluid of Erupting Primary Teeth Correlated With Systemic Disturbances Accompanying Teething

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Abstract

Purpose: The aim of this study was to investigate whether there are increased levels of the inflammatory cytokines IL-1ß, IL-8, and TNFα in the gingival crevicular fluid (GCF) of erupting primary teeth. This increase could explain such clinical manifestations as fever, diarrhea, increased crying, and sleeping and eating disturbances that occur at this time.

Methods: Sixteen healthy children aged 5 to 14 months (mean=9.8 months) were examined twice a week over 5 months. Gingival crevicular fluid samples were taken from erupting teeth. As a control, GCF was collected from the same teeth 1 month later. Cytokine production was measured by ELISA. Signs and clinical symptoms were listed. Pearson correlation coefficients were used in the comparisons described below. A paired t-test was used to analyze the same variable at different times.

Results: Fifty teeth of the 16 children were studied. GCF samples were collected from 21 of these teeth. Statistically significant differences (P<.05) were found with regard to the occurrence of fever, behavioral problems, and coughing during the teething period and the control period. During the control period, 72% of the children did not exhibit any clinical manifestations, whereas during the teething period only 22% of the children did not exhibit any clinical manifestations. The study revealed high levels of inflammatory cytokines during the teething period, with a statistically significant difference in TNFα levels (P<.05) between the teething period and the control period. Correlations were found between cytokine levels and some of the clinical symptoms of teething: IL-1ß and TNFα were correlated with fever and sleep disturbances; IL-8 and IL-1ß were correlated with gastrointestinal disturbances; IL-1ß was correlated with appetite disturbances.

Conclusions: Cytokines appear in the GCF of erupting primary teeth. The cytokine levels are correlated to some symptoms of teething. (Pediatr Dent. 2003;25:441-448)

Keywords: teething, cytokines, gingival fluid, primary tooth eruption

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accompanying teething (eg, drooling and behavioral changes) and the normal physiological changes that occur at that age.

Conflicting opinions have been reported regarding symptoms caused by teething. Tasanen\(^7\) found that the only symptoms caused by teething were restlessness during the day, increased thumb-sucking, itching gums, and drooling. On the other hand, Jaber et al.\(^4\) in a controlled clinical study of 46 healthy babies, found that there were grounds for claiming that the eruption of the first tooth is accompanied by a fever of over 37.5°C. Honig\(^5\) found that one third of the pediatricians in Philadelphia also thought that a fever of over 38°C could be caused by teething. Nelson\(^6\) wrote in his pediatric textbook that the possible occurrence of infection and sensitivity when the tooth erupts through the gingiva. Macknin et al.\(^7\) stated that before caregivers attribute any signs or symptoms of a potentially serious illness to teething, other possible causes must be ruled out. Ramos\(^8\) suggested that symptoms of teething can cause systemic infections. Although some recent articles suggest a relationship between teething and systemic manifestations of inflammation, no scientific basis for the appearance of these signs and symptoms has yet been investigated.

Shapira et al.\(^9\) hypothesized that teething, along with the associated gingival trauma, can cause the release of inflammatory cytokines and the accompanying systemic signs. Cytokines are small proteins involved in local inflammation or immunoregulation.\(^10\) When there is an inflammation, IL-1ß is the major “endogenous pyrogen” that may contribute to tissue damage by stimulating the release of neutral metaloproteinases from fibroblasts and other mesenchymal cells; it can also induce the production of high levels of many other cytokines, including its antagonist IL-1RA\(^10,11\) and can affect connective tissue remodeling. Cytokines include the many interleukins (ILs), tumor necrosis factors (TNFs), interferons (IFNs), polypeptide growth factors (GFs), and colony-stimulating factors (CSFs).\(^12\) Epithelial cells and macrophages make up a significant part of periodontal tissue, and it has been demonstrated that these cells secrete IL-1ß, IL-6, and TNFα.\(^12\) Dinarello\(^13,14\) found high levels of IL-1ß and TNFα in a wide range of clinical situations mostly associated with high fever, and a direct correlation was found between systemic IL-1ß levels and the severity of inflammatory diseases.

Studies have shown a direct association between gingivitis and an increase in the production of IL-1ß in the gingival crevicular fluid (GCF) surrounding the teeth.\(^15,16\) Blakey et al.\(^10\) also found an increase in IL-1ß levels in the GCF of primary teeth, immediately upon or around the time of tooth eruption. Indeed, Graves et al.\(^17\) in their study published in June 2002, suggested that TNF receptor signaling can affect tooth eruption by acting as a monocyte survival signal in some areas of bone that are undergoing developmentally regulated remodeling.

The aim of the present study was to investigate whether there is a correlation between the inflammatory cytokines IL-1ß, IL-8, and TNFα in the GCF of primary teeth, immediately upon or around the time of tooth eruption. This is the first time that a study is being conducted on the relationship between teething, inflammatory cytokine production, and clinical symptoms.

### Methods

#### Study sample

The study sample consisted of 16 healthy infants-7 girls and 9 boys-who attended the Na'amat Day Care Center in Hadasah Hospital, Jerusalem, Israel. Their ages ranged from 5 to 14 months, with a mean age of 9.8 months. The children were under observation for a period of 5 months.

During the study period, 72 teeth erupted. Of these, 22 teeth were excluded because the children were suffering at the time from diagnosed medical conditions such as respi-
cillary infections (asthma, pneumonia, and bronchiolitis), ear infections and viral infections, or they had recently been vaccinated. The remaining 50 teeth were examined for the presence of systemic manifestations. Out of these 50 teeth, the authors could not collect GCF samples from 29 teeth for the following reasons:
1. More than 1 tooth had erupted at the same time.
2. A tooth had erupted during the control period.
3. Technical reasons interfered (eg, the infant didn’t show up).

GCF samples were thus collected and studied from 21 teeth. Parents of all of the children participating in the study signed an informed consent form approved by the Hadassah Medical Center’s Helsinki Committee and Israel’s Ministry of Health.

All the children within this age group in the day care center were examined twice weekly by the same pediatric dentist. The teething period was defined according to Macknin7 as 1 to 3 days before, on the day of, and 1 to 3 days after tooth eruption. Although “eruption” is a continuum or a process by which the forming tooth comes into its final occlusion, the teething period in this study refers to the period involving “the act of breaking out, appearing, or becoming visible, as eruption of the teeth.”31

Fluid from the sulcus was collected on the day of eruption or on 1 of the following 3 days. GCF samples were collected with the same periopaper strip from the buccal, lingual, or palatal sites of the erupting tooth. GCF was again collected from the control group (ie, from the same tooth 1 month later), and later noted were the clinical manifestations exhibited 1 to 3 days before, on the day of, and 1 to 3 days later. For the sake of convenience, samples were taken only from anterior teeth. After isolating the tooth with a cotton roll, GCF was collected with a periopaper strip (M arco) and positioned at the orifice of the sulcus for a total of 30 seconds, and the amount of harvested liquid was measured with a Periotron 6000 (H arco Electronics, Irvine, Calif). Each strip was placed in a 0.5% Phosphate Buffered Saline bovine solution and stored at –20°C.

The systemic manifestations occurring during this period were listed. The following signs and symptoms were recorded: (1) fever; (2) vomiting; (3) gastrointestinal disturbances; (4) drooling; (5) behavioral problems (eg, irritability during daytime, increased crying, restlessness); (6) sleep disturbances (sleeping less, awakening during sleep, crying during sleep); (7) coughing; (8) appetite disturbances; and (9) biting (on teething rings) and/or (increased) sucking. A child with a temperature of under 37.5°C was classified as having “no fever.” A temperature of 37.6°C to 38.5°C was regarded as low/moderate fever, and a temperature over 38.5°C was classified as high fever.

The children’s signs and symptoms for each day were recorded by the examining dentist on the basis of the information provided by parents as well as caregivers at the day care center. Each manifestation was then classified as normal or abnormal. Any appetite, sleep, behavior, or gastrointestinal change was classified as abnormal.

### Table 1. Systemic Manifestations During Tooth Eruption Period and Control Period (Paired t Test, n=50, df=49)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tooth eruption %</th>
<th>Control %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>24</td>
<td>8</td>
<td>0.04</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disturbances</td>
<td>10</td>
<td>2</td>
<td>0.10</td>
</tr>
<tr>
<td>Drooling*</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Behavioral problems</td>
<td>50</td>
<td>16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>18</td>
<td>8</td>
<td>0.13</td>
</tr>
<tr>
<td>Coughing</td>
<td>12</td>
<td>2</td>
<td>0.06</td>
</tr>
<tr>
<td>Appetite disturbances*</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Biting and/or sucking</td>
<td>4</td>
<td>6</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*No comparisons could be performed between the 2 periods due to lack of observation during the control period.

### Table 2. Comparison Between Systemic Manifestations and Cytokine Levels During Tooth Eruption Period and Control Period (Paired t Test)

<table>
<thead>
<tr>
<th>Variable</th>
<th>P Values df  t Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>0.04* 49 2.06</td>
</tr>
<tr>
<td>Gastrointestinal disturbances</td>
<td>0.10 49 1.66</td>
</tr>
<tr>
<td>Behavioral problems</td>
<td>&lt;0.01* 49 3.84</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>0.13 49 1.53</td>
</tr>
<tr>
<td>Coughing</td>
<td>0.06* 49 1.94</td>
</tr>
<tr>
<td>Biting and/or sucking</td>
<td>0.66 49 -0.44</td>
</tr>
<tr>
<td>IL-18</td>
<td>0.85 19 0.19</td>
</tr>
<tr>
<td>IL-8</td>
<td>0.85 19 0.19</td>
</tr>
<tr>
<td>TNFα</td>
<td>&lt;0.01* 20 3.21</td>
</tr>
</tbody>
</table>

*Indicates statistically significant differences between the 2 periods (P<.05).

### Statistical methods

Pearson correlation coefficients were used for the comparisons described that follow. Paired t tests were used for analyzing the same variable at different time periods.

### Evaluation of cytokines levels

GCF levels of cytokines IL-18, IL-8, and TNFα were measured by a solid phase ELISA, using high sensitive immunoassay kits (Q uantikine H S R & D). The assay technique utilize an amplification system in which the alkaline phosphatase reaction provides a cofactor that activates a redox cycle leading to the formation of a colored product.
Results

A total of 16 children participated in the study (7 girls and 9 boys). A total of 50 teeth were studied, and GCF samples were collected from 21 of them. This study is the first to report and measure TNF, IL-1, and IL-8 from the samples. It was also the first to report and measure TNF, IL-1, and IL-8 from the GCF of 1 tooth. The mean IL-1 was 30 pg (SE ±6) for an erupting tooth and 28 pg (SE ±7) for the control. The mean IL-8 level was 118 pg (SE ±31) for the erupting primary incisors and 106 pg (SE ±24) for the control. TNF mean values were 39 pg (SE ±2) for the erupting tooth and 32 pg (SE ±1) for the control.

The secondary enzyme system consists of alcohol dehydrogenase and diaphorase (amplifier). A “sandwich” enzyme immunoassay technique is used. A curve is plotted of the optical density vs the concentration of given interleukin in the standard wells. By comparing the optical density of the samples to this standard curve, the concentration of the interleukin in the survey samples was then determined.

ELISA kits were purchased from Research and Diagnostic Systems (R&D, Minneapolis, Minn), as reported elsewhere.11,32

Table 3 presents the percentages of systemic clinical disturbances during tooth eruption and during the control period. There were statistically significant differences (P < .05) between the periods with regard to fever, behavioral problems, coughing, and TNF levels.

The correlations between inflammatory cytokine levels and the occurrence of clinical manifestations are presented in Table 3. During the first period, correlations were found between high levels of IL-1ß and fever, gastrointestinal disturbances, sleep disturbances, and appetite disturbances. During the same period, a correlation was observed between high levels of IL-8 and gastrointestinal disturbances, sleep disturbances, and appetite disturbances. No correlation was found between any type of cytokine release and vomiting; the vomiting was therefore excluded from the table. In the control period, no correlation was found between any type of cytokine release and gastrointestinal disturbances, drooling, and appetite disturbances. On the other hand, during this period correlations were found between IL-1ß and IL-8 levels and sleep disturbances and fever.

Table 4 presents fever levels during the period of tooth eruption and the control period. The differences between the 2 periods were found to be statistically significant (paired t test), P = .04.

Table 1 presents the percentage of infants with clinical manifestations during the 2 periods. During the teething period, behavioral problems were observed in 50% of the infants, compared to 16% in the control period (P < .01); fever was observed in 24% of the infants during tooth eruption and in 8% of the infants during the control period (P = .04); and coughing was observed in 12% during tooth eruption compared to 2% (P = .06) of the infants during the control period. The authors could not compare manifestations of vomiting, drooling, and appetite disturbances due to the absence of observations during the control period.

Table 2 presents a comparison (paired t test analysis) between systemic manifestations and cytokine levels during teething and the control period. There were statistically significant differences (P < .01) between the periods with regard to fever, behavioral problems, coughing, and TNF levels.

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in Table 5. During the control period, 72% of the children did not display any clinical manifestations, whereas during the teething period only 22% of the children did not display any clinical manifestations. The differences among the distribution of the systemic manifestations between the 2 periods were found to be statistically significant ($P < 0.01$).

Figure 1 presents the levels of inflammatory cytokines during the 2 periods: (1) during tooth eruption; and (2) 1 month later. There was a decrease in mean levels of inflammatory cytokines in the control period, which was found to be statistically significant for TNF-α but not for IL-1β and IL-8.

**Discussion**

This is the first study documenting a correlation between the release of inflammatory cytokines from periodontal tissue during tooth eruption and systemic manifestations observed during this period.

The study's findings correlating systemic manifestations with teething, confirm those of Tasanen\(^7\) and Macknin.\(^7\) Tasanen\(^3\) found that tooth eruption was linked to daytime restlessness, thumb-sucking, gum rubbing, drooling, and perhaps a loss of appetite. Macknin\(^7\) performed a large prospective study of infant teething and found increased biting, drooling, gum rubbing, sucking, irritability, wakefulness, ear rubbing, facial rash, decreased appetite for solids, and mild temperature elevation during that period. Seward\(^33\) found that general irritability was the most common disturbance that occurred during the eruption of the primary teeth. Both Jaber\(^4\) and Galili\(^34\) found a correlation between teething and fever of over 37.5°C.

The results of the present study show a higher percentage of systemic manifestations during the eruption period than during the control period, with statistically significant differences between the 2 periods ($P < 0.05$) with regard to fever, behavioral problems, and coughing. There were no statistically significant differences in biting and/or sucking and sleep disturbances. These results do not conform to those of Tasanen,\(^3\) who found that coughing was not related to teething, but they do conform to the findings of Macknin,\(^7\) who found that teething was not related to gastrointestinal disturbances.

Carpenter,\(^35\) in his study conducted at a well-baby clinic of a university hospital, found that 38% of the patient sample exhibited none of the disturbances associated with teething, 39% exhibited 1 disturbance, and 23% exhibited 2 or more disturbances concurrent with the teething experience. In the present study, during the teething period 22% displayed no disturbances, 32% had only 1 disturbance, 26% exhibited 2 disturbances, and 20% exhibited 3 disturbances. On the other hand, during the control period 72% exhibited no associated disturbances.

Shapira et al\(^9\) reported a case showing that teething may also trigger acute graft-versus-host (GVH) disease, as manifested twice in an infant who was undergoing a bone marrow transplant during teething, and which was resolved only upon completion of tooth eruption. They suggested that IL-1β secretion might be the mechanism for the aggravation of GVH disease during tooth eruption. Their discovery triggered the idea that led to the present study.

IL-1β is a cytokine thought to be a major mediator of pathophysiological events in many acute and chronic inflammatory diseases. IL-1β is the major "endogenous pyrogen" that may contribute to tissue damage by stimulating the release of neutral metalloproteinases from fibroblasts and other mesenchymal cells.\(^11\)

In the present study, a correlation was found between the release of inflammatory cytokines and teething symptoms. The release of IL-1β during teething was correlated with fever, GI disturbances, sleep disturbances and appetite disturbances. IL-8 was correlated with GI disturbances, and TNF-α release was correlated with sleep disturbances, and fever. In the control period, IL-1β was again correlated with fever, behavioral problems, and sleep disturbances, IL-8 was correlated with fever and sleep disturbances, and TNF-α was correlated with coughing. The number of disturbances decreased in the nonteething control period compared with the tooth eruption period.

There was a decrease in mean levels of inflammatory cytokines during the control period compared with the study period. This difference was found to be statistically
significant only for TNFα but not for IL-1β and IL-8, although the same trend was observed for all 3. The nonstatistically significant findings may have been the result of the fact that the eruption process is a long one (longer than a month). Had the second sampling been conducted more than a month after eruption, perhaps the difference between the teething and control periods would have been even greater.

The findings may also have been due to the small number of children studied because of the dropout of children from whom the authors could not obtain the GCF sample. There may also have been great variability between the 2 samples as a result of the difficulty of isolating the sampled teeth for 30 seconds to minimize saliva contamination.

A previous study measuring TNF in the GCF of normal primary molars has reported a mean of 91 pg/site.36 Possible explanations for the lower values found in this study might be:

1. the larger volume or quantity per site of GCF retrieved from a matured primary molar in children 7 to 12 years of age compared to the GCF/mL in the infant’s primary incisors, as in the present study;
2. the different techniques used in both studies.

Whereas in the Ureles study,36 an immunomagnetic technique was used to retrieve TNF-absorbing the cytokine present in the GCF and probably in the surrounding tissue—the authors used paper strips that absorbed the TNF from the GCF only.

Indeed, Rossomando et al37 compared both techniques and concluded that the immunomagnetic method was more effective at retrieving TNF, showing higher average values than with paper strips, as used in the present study. However, the authors nevertheless used paper strips in the present study because it obtained fluid specifically from the gingival crevice and not from the surrounding area.

Ureles et al36 were the first to measure TNF levels in GCF of normal primary molars. Interestingly enough, they found that the TNF levels were 1.6 times higher from the crevice of ankylosed primary molars than from normal primary molars and 2.6 times higher from the crevice of molars missing their permanent successor. The explanation they offered for the results of that study was pertinent to the present study. They suggested that the higher values of TNF reflect the degree of inhibition of osteoclastic activity in both the ankylosed and the missing permanent successor since the TNF receptors in those 2 examples were blocked or inactivated. Therefore, the overproduced TNF was carried into the crevice by normal flow of crevicular transudate.

In the present study, the higher levels of TNF in the GCF of the erupting incisors, compared to the same teeth 1 month later, highlight the important role of TNF and other cytokines in the erupting process. It has been shown that the eruption process is preceded by an influx of mononuclear cells into the dental follicle and the release of cytokines (including TNF, IL-1, and IL-8), prostaglandins, and growth factors, which initiate the formation of the preosteoclasts necessary for creating an eruption process.

In their recent publication, Wise & Yao41 suggested that TNF, in addition to its synthesis in tooth eruption, is synthesized by the periodontal ligament cells as well, and, therefore, may be related to periodontal disease.

The authors’ results revealed high levels of cytokines, with statistically significant high levels of TNF in the gingival crevicular fluid derived from the periodontal ligament of erupting teeth during the teething period. In addition, correlations were found in this study between cytokine levels and some of the clinical symptoms of teething, especially with fever, the only quantifiable systemic factor.

As serum cytokine levels were not measured in this study, the question arises as to whether these local GCF increased levels of cytokines actually cause the systemic manifestations during tooth eruption.

The elevation of body temperature in response to disease has interested both clinicians and cellular biologists, and only recent advances have provided the evidence that fever is the systemic response of the body to the presence primarily of proinflammatory cytokines, IL-1, and TNF.13,14 Fever is the result of a cascade of events that begins with pathologic infection, the lipopolysaccharide (LPS) of the bacterial wall, or the synthesis and release of cytokines in the body by activated monocytes. The biological response to LPS is indistinguishable from the response to pyrogenic cytokines IL-1 or TNF. Both enter the circulation and reach the endothelial cells of the hypothalamus. From these cells, prostaglandin E-2 (PGE-2) is released into the brain and binds to a specific receptor, EP-3, on cells in the hypothalamic thermoregulatory center. The PGE-2 induces the release of cyclic AMP, which then acts to raise the thermostatic set-point from normal levels to elevated levels. The elevated set-point results in mechanisms of peripheral heat conservation (vasoconstriction) as well as increased metabolic heat production, until the temperature of the blood that bathes the hypothalamus matches the elevated set point, resulting in fever.13

Thus, the present study is the first to demonstrate the role of local cytokines present in the GCF of erupting teeth and correlate them with systemic disturbances during teething. Additional studies are needed with a larger number of children to clarify the role of these proinflammatory cytokines in tooth eruption pathogenesis.

**Conclusions**

1. Cytokines are found in the GCF fluid of teeth during the eruption period. The gingival crevicular fluid TNFα is significantly elevated during the teething period, and other cytokines were mildly elevated.

2. The GCF cytokines are correlated to some of the clinical symptoms of teething. IL-1β and TNFα are correlated with fever and sleep disturbances, IL-1β and IL-8 with gastrointestinal disturbances, and IL-1β with appetite disturbances.
References


In recent years, there has been an emphasis on relatively short-term studies to provide an early prediction of clinical success of posterior composite resins. However, longer-term studies are needed to identify the modes of composite failure and to compare the expected lifespan of posterior composite resin restorations with that of amalgam restorations. This report gives the 7-year clinical findings of 3 different posterior resin composites. The study reports the success and failure of each composite type and explores the possible relationship between failure and salivary levels of specific bacteria. A total of 120 restorations were placed in premolars and permanent molars (88 Class I, 32 Class II). All restorations were placed by the same operator using the same technique for each restoration. The following resin composites were used: Z100 (3M Dental), Clearfil Ray-Posterior (Kuraray), and Prisma TPH (Caulk/Dentsply). All dentinal surfaces were covered with a glass ionomer base prior to composite placement and restorations were evaluated using UPHS criteria. The evaluations were done by 3 clinicians trained in the technique and not involved in the treatment procedures. Changes in the parameters during the 7-year period were evaluated and statistical differences were measured with the Cochran Q and Friedman test. The level of significances was $P < 0.05$ for all evaluations. Seventy restorations were available for evaluation after 7 years. All materials had significant marginal adaptation problems at the 7-year ratings, but there was no significant difference among the materials in regard to color match, anatomic form, and secondary caries. The mean failure rate was 4.3% for Z100, 3.8% for Clearfil Ray-Posterior, and 9.5% for TPH; however, there was no significant difference between the mean failure rates of the three composites tested. The authors report that there appeared to be no relationship between the levels of bacteria present and failed restorations. The main modes of failure of the composites were secondary caries and marginal adaptation problems. There was no significant difference in the mean failure rates of the composites tested, and there was no connection between the levels of mutans streptococci and lactobacilli in the saliva and the failure rates.

Comments: While the authors suggest that the time of replacement for posterior resin composites may be prolonged to more than 7 years, it is unclear whether or not this suggestion is fully supported by the study in terms of the number of surfaces restored. The authors report 7-year results from 70 restorations; however, the specific number of each type of restoration (Class I or Class II) is not available. Consequently, the suggested conclusions may not apply to all classes of posterior composite resin restorations. BB

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43 references