SERUM INTERCELLULAR ADHESION MOLECULE-1 AND INTERLEUKIN-10 IN ASTHMATIC CHILDREN

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Abstract

The objective of the present study was to investigate serum intercellular adhesion molecule-1 (sICAM-1) and interleukin-10 (IL-10) in asthmatic children in correlation with immunoglobulin E (IgE). Thirty asthmatic children and ten controls were enrolled. Using enzyme linked immunosorbent assay (ELISA), sICAM-1, IL-10 and total IgE levels were determined during acute attacks, and 2 weeks after remission (stable asthma). The results of the present study showed that sICAM-1 and total IgE increased significantly in children during acute attacks Vs controls (P<0.05), while IL-10 decreased significantly in children during acute attack Vs controls (P<0.05). On the other hand, in stable asthma sICAM-1, IL-10, and total IgE all return to levels comparable with controls. IL-10 correlated significantly in a negative manner with sICAM-1 and total IgE levels. While sICAM-1 correlated positively with total IgE levels. Conclusion: We can conclude that sICAM-1 might play a remarkable Pathophysiology role in controlling the severity of asthmatic paroxysm, whereas IL-10 is protective against asthma. The present data open the door in the very near future for therapeutic intervention in pediatric asthma using anti-inflammatory agents could act by blocking ICAM-1 molecules and administration of IL-10 as a novel therapy.

Introduction

Bronchial asthma is by far the commonest of all chronic diseases in children (Godfrey, 1992). According to the International Consensus Report (1992), asthma is a chronic inflammatory disorder of bronchi. It is characterised by
bronchial hyperactivity to a variety of stimuli in which many cells play a role including mast cells and eosinophils (Paganin et al., 1996).

The IgE response is a local event occurring at the site of allergen entry at mucosal surfaces and at local lymph nodes. Levels of IgE are raised in atopic individuals and even more so in those with parasitic infections, when considering the possibility of atopic disease, a raised level of IgE aids the diagnosis but a normal level does not exclude it (Brostoff and Scadding, 1991).

Serum ICAM-1 was reported to be elevated in patients with some inflammatory disorders and the enhanced release of proinflammatory cytokines seems to be related to the elevated level of serum ICAM-1 in these disorders (Shijubo et al., 1992).

Serum ICAM-1 has been shown to be active in recruitment of eosinophils, suggesting a significant role in allergic disorders, and also in the activation of T-cells which is an event to involve the interaction between sICAM-1 and lymphocyte function associated antigen (Wegner et al., 1990).

El-Gazzar and El-Shaier (1997) found that antigen inhalation produced increased expression of sICAM-1 on the bronchial endothelium and airway epithelium of the animals. Therefore, it is probable, that sICAM-1 participates in the recruitment of eosinophils to asthmatic airways and contributes in the pathogenesis of asthma.

IL-10 is an anti-inflammatory cytokine with a down regulating character influencing inflammatory process. The role of IL-10 in allergic inflammation is supported by its ability to inhibit IgE production, shorten eosinophil survival, and induce allergen specific tolerance (Moore et al., 1993).

**AIM OF THE WORK**

The objectives of the present study were to investigate the sICAM-1 and IL-10 in asthmatic children (during asthmatic paroxysm and stable state '2 weeks after remission'), and to correlate between them and IgE response in those children.
Subjects And Methods

Subjects:

(a) Patients (Groups I) : 30 asthmatic children in acute attacks. They included 21 boys and 9 girls, aged 4-11 years (mean 9.2 ± 1.4 years). On admission, the severity of the asthmatic paroxysm was mild in 8 children, moderate in 10 children and severe in 12 children. According to the frequency of the paroxysm, 9 patients had infrequent episodic asthma (IE), i.e. no more often than once per week, 12 had frequent episodic (FE), i.e. more than once per week and 9 had chronic asthma, i.e. daily wheezing with frequent exacerbation (classification was done according to Scadding, 1992). All children were atopic (i.e. had positive skin prick test).

(b) Controls (Group II) : 10 healthy children aged 4-10 years (mean 9.2 ± 1.4 years), 7 boys and 3 girls, descendants of non atopic families served as controls.

Care was taken to exclude children with history of respiratory infections or parasitic infestations in the last two weeks.

Methods:

(1) Beside clinical evaluation a set of investigations were done including: postanterior plain x-ray chest, urine and stool analysis, skin prick test using a battery of common environmental allergens and some foods using Hollis Steir extract; forced expiratory volume in one second (FEVI), using computerized spirmometer (Vica test P2A, Mijnardt, Bunnik Molland) and arterial blood gases (using AVL 993 machine, Austeria).

(2) Serum ICAM-1, IL-10 and total IgE were measured on admission, and 2 weeks following remission of the asthmatic paroxysm (stable asthma).

* Quantitative determination of serum ICAM was done by Sandwich Enzyme Immunoassay (using Biosource
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Corporation. Fleurus, Belgium).

* Quantitative determination of serum IL-10 was done by Enzyme-linked Immunoasay using (Predicta Co., Cat # KH CO 100-SB).

* Quantitative determination of serum total IgE was done by Enzyme-linked Immunoasay (using Kallestade, Diagnostics Chaska).

**Results**

The clinical characteristics of the subjects enrolled in the study are illustrated in table (1).

* The levels of sICAM-1, IL-10 and total IgE in controls and children with asthma and correlation of results are illustrated in table (2) and figures (1), (2) & (3).

* Correlations between IL-10 and sICAM-1 is illustrated in Figure (4).

* Correlations between sICAM-1 and FEV-1, PaCO2 & total IgE are illustrated in figures (5), (6) & (7) respectively.

* Correlations between IL-10 and FEV-1, PaCO2 & total IgE are illustrated in figures (8), (9) & (10) respectively.

Table 1: Characteristics of Children with Bronchial Asthma and Controls.

<table>
<thead>
<tr>
<th>Character</th>
<th>Total (30)</th>
<th>Patients with Bronchial Asthma (28)</th>
<th>Control (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild (8)</td>
<td>Moderate (12)</td>
<td>Severe (12)</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>9.2±1.4</td>
<td>8.7±1.3</td>
<td>7.1±1.6</td>
</tr>
<tr>
<td>Sex (Boy/Girl)</td>
<td>2.33</td>
<td>0.9</td>
<td>1.7*</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>66.9±12.2*</td>
<td>88.9±10.8*</td>
<td>72.0±18.2*</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>65.8±12.3*</td>
<td>83.0±8.7</td>
<td>87.2±22.0*</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>45.8±6.6*</td>
<td>43.8±4.8*</td>
<td>50.8±4.2</td>
</tr>
<tr>
<td>Positive Skin Prick Test (%)</td>
<td>30*</td>
<td>26.7*</td>
<td>33.3</td>
</tr>
</tbody>
</table>

IE: Infrequently episodic
FEV1: Forced expiratory volume in one second.
PaO2: Partial arterial oxygen pressure
PaCO2: Partial arterial carbon dioxide pressure
* Significant vs mild attack
* Significant vs moderate attack
* Significant vs severe asthma
* Significant vs control
Table 2: Results of sICAM-1, IL-10 and total IgE in asthmatic children and controls.

<table>
<thead>
<tr>
<th>Character</th>
<th>Total (30)</th>
<th>Patients with bronchial asthma (30)</th>
<th>Control (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Severity of acute paroxysm</td>
<td>Frequency of acute attack</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>sICAM-1 (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- During attack</td>
<td>727.7±110.9</td>
<td>531.6±211.8</td>
<td>542.1±390.5</td>
</tr>
<tr>
<td>- After 2 weeks</td>
<td>411.8±211.7</td>
<td>361.7±251.1</td>
<td>592.8±271.6</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- During attack</td>
<td>6.4±1.5</td>
<td>8.1±2.3</td>
<td>7.4±1.8</td>
</tr>
<tr>
<td>- After 2 weeks</td>
<td>14.6±3.1</td>
<td>15±4.1</td>
<td>12±3.1</td>
</tr>
<tr>
<td>Total IgE (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- During attack</td>
<td>288.8±40.1</td>
<td>201.6±100.1</td>
<td>356.4±192.6</td>
</tr>
<tr>
<td>- After 2 weeks</td>
<td>156.4±45.3</td>
<td>105.7±50.7</td>
<td>181.6±40.7</td>
</tr>
</tbody>
</table>

IE: Infrequently episodic
IE: Significant vs mild attack
IE: Significant vs FE asthma
IE: Significant vs control

Fig. (1): sICAM-1 in different groups of children with asthma vs controls

Fig. (2): IL-10 in different groups of children with asthma vs controls

Fig. (3): Total IgE in different groups of children with asthma vs controls

Fig. (4): Correlation between IL-10 and sICAM-1 (r=0.88 & P<0.05)
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Fig. (5): Correlation between sICAM-1 and PaCO2 in acute asthmatic children ($r = -0.61$ & $P < 0.05$)

Fig. (6): Correlation between sICAM-1 and FEV1% predicted value in acute asthmatic children ($r = -0.60$ & $P < 0.05$)

Fig. (7): Correlation between sICAM-1 and total IgE in acute asthmatic children ($r = -0.62$ & $P < 0.05$)

Fig. (8): Correlation between IL-10 and FEV1% predicted values in acute asthmatic children ($r = -0.67$ & $P < 0.05$)

Fig. (9): Correlation between IL-10 and PaCO2 in acute asthmatic children ($r = -0.72$ & $P < 0.05$)

Fig. (10): Correlation between IL-10 and total IgE in acute asthmatic children ($r = -0.75$ & $P < 0.05$)

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Discussion

Bronchial asthma is a complex disorder which can not be defined adequately in terms of university acceptable and comprehensive definition (Phelan et al., 1994).

In the present work, the elevated levels of sICAM-1 in asthmatic children was in agreement with results reported in adult asthmatics by El-Gazzar and El-Shaier, (1997).

But, in contrast with those reported by Ceyan et al., (1995) who found insignificant elevation of sICAM-1 in children with acute asthma and found unsatisfactory explanation for their results and advised for more work. But, it could be suggested that the difference in study population may be responsible for that controversy with the present results.

The elevated concentration of sICAM-1 in acute asthmatic paroxysm may reflect the extent of expression of ICAM-1 molecules on bronchial epithelial cell. The mechanism and significance of increased expression of ICAM-1 molecules on asthmatic bronchial epithelium is unclear (Suzanne et al., 1996).

Greve et al., (1989) suggested that the increased expression of ICAM-1 molecules on asthmatic bronchial epithelium in children with acute asthma, is related to the association of ICAM-1 with human rhino virus (HRV) infection, a common allergic virus in children. Cell-bound ICAM-1 is the vehicle through which the major classes of HRV enter epithelial cells. Also, they suggested that ICAM-1 contribute to a great extent to inflammatory infiltrate association with HRV infection that commonly precipitates asthmatic paroxysms in children.

Calderon et al., (1992) suggested that, inflammatory cytokines released in acute asthmatic paroxysms, including IL-1, IL-2 and TNF α act as endothelial activators. These endothelial activators induce the expression of ICAM-1 molecules on the surface of endothelial cells that in turn increase the adhesive properties of the endothelium for leucocyte.
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The above mentioned data highlight the remarkable pathophysiologic role of ICAM-1 in reproducing inflammatory infiltrate in both acute asthmatic paroxysms and chronic asthma in children. And, also pinpointed to the great need to down regulate the increased expression of ICAM-1 molecules on asthmatic airways as a novel anti-inflammatory therapy that may help to reduce asthma-related morbidity and mortality in children.

Recently, many therapeutic trials had been done, all directed at down-regulating increased expression of ICAM-1 molecules in asthmatic airways (Nagase et al., 1995), specific blocking of adhesion molecules by monoclonal antibodies, anti-adhesive molecules therapy, may complement the asthmatic anti-inflammatory treatment and appears to show great promise (Barness and Pajet, 1997).

These results are supported by Burrows et al., (1991), who found that bronchial asthma was linked to serum level of total and specific IgE even without apparent clinical symptoms and signs.

Sarno et al., (1994) found that ICAM-1, increased on the vascular endothelial cells and bronchial epithelial cells especially after activation by histamine also, he found that increased expression of ICAM-1 on bronchial epithelium of asthmatic patient increase the stage of asthma.

Wegner et al., (1990) found that high level of ICAM-1, was presented in bronchial and vascular epithelial cells after allergen exposure, there is eosinophil rich inflammatory infiltrate and non-specific bronchial hypersensitivity. Also, he found that administration of anti-ICAM-1 antibodies causes simultaneous reduction of eosinophil infiltrated bronchial hypersensitivity.

Lassale et al., (1993) found that there was a close cooperation between the endothelial cell, macrophages T-cells and mast cells that support the idea that adhesion molecule specially ICAM-1 constitute a prime target for the treatment of the allergic inflammatory reaction.
The current data indicated that, serum IL-10 decreased significantly during acute bronchial asthma. This is supported by the study of Bonfield et al., (1993) who found a diminution in the level of IL-10 in status asthmatics in BAL samples. Also, John et al., (1998) found that production of IL-10 decreased in bronchoalveolar lavage and peripheral blood mononuclear cells of patients with asthma. This could explain the unbalanced high proinflammatory cytokine reaction at this time that could lead to the development of more severe disease.

IL-10 expression is therefore, diminished in patients with prolonged attacks of asthma and its presence in normal subjects may contribute that those subjects are tolerated and no attacks can present in them. This supported by Cezmi et al., (1998) that useful IL-10 as immunotherapeutic cytokine to limit the hypersensitivity states.

As regards to the severity of the disease and total IgE, it was found that they are closely related to each other and this in agreement with Barnes et al., (1992).

Conclusion

1. The present data suggested that sICAM-1 might play a remarkable pathophysiologic role in controlling severity of asthma this may be through reproducing inflammatory infiltrate in acute asthma in children.

2. The present data highlight the great need to down-regulate the increased expression of sICAM-1 molecules on asthmatic airways.

3. The present data highlight the protective role of IL-10
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against asthma in children.

4. The present data open the very near future for possible therapeutic interventions in pediatric asthma using novel anti-inflammatory agents could act by blocking ICAM-1 molecules and IL-10 therapy. They might help in reducing the currently increased asthma related morbidity and mortality in children.

References


Sarno M., Allen J. and Rodon-
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