# Serum soluble interleukin-2 receptor (IL-2R) in children with allergic disorders

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## INTRODUCTION

Inflammatory responses play a central role in a variety of allergic disorders. These inflammatory responses are complex and may involve several immunologic pathways.[1-4] It is now recognized that T-cells may influence a variety of these pathways. The T-cell-derived lymphokine, interleukin-2 (IL-2), plays a pivotal role in the regulation of many T-cell mediated responses and interacts with a high-affinity interleukin-2 receptor (IL-2R), which is expressed on a variety of cell types.[5, 6] Activation of lymphoid cells is associated with secretion of IL-2 and with the expression of high affinity IL-2R, which are composed of at least three chains ($\alpha$, $\beta$, $\gamma$) each interacting with distinct epitopes on the IL-2 molecule. We have previously reported[7] that the activation process is associated with the release of one of these chains, the Tac peptide or soluble IL-2R (sIL-2R). This soluble form of the IL-2R is slightly smaller than the cell-membrane-associated form of the same molecule, and is fully capable of binding IL-2. Studies in a number of inflammatory diseases including autoimmunity, AIDS, and allograft reaction have shown that levels of soluble Tac protein in serum and other secretions correlate with immunologic activation and inflammation processes occurring in vivo.[8] In the present study we assessed IL-2R levels in the sera of children with allergic disorders.

## SUBJECT AND METHODS

Blood samples were obtained from five groups: seven subjects aged 1–10 years with severe atopic eczema, seven subjects aged 2–10 years with mild atopic eczema, seven subjects aged 5–10 years with severe asthma, seven subjects aged 4–8 years with mild asthma, and seven normal subjects aged 1–13 years. Assignment to mild or severe asthma was based upon criteria reported elsewhere.[9] Similarly, the scoring system proposed by Sampson and McCaskill[10] was applied to patients with eczema. Those with a score ≤2+ were classified as affected with mild eczema, while children with a score of 3+/4+ were grouped as affected with severe eczema.

Specific diagnoses were established on the basis of family and personal history, physical examination, and clinical follow-up. None of the patients had been receiving steroids or other antiinflammatory drugs over 2 months before blood collection. Informed consent was obtained from children's parents.

*Blood Collection*

Five milliliters of peripheral blood was collected from each patient and promptly centrifuged for serum separation. Serum was either immediately processed for biochemical evaluation or stored in small aliquots (0.5 mL) at −70 °C until used.

*Evaluation of IgE-mediated hypersensitivity*

For each patient, IgE-mediated hypersensitivity was evaluated by prick-test, as well as by total (PRIST) and specific (RAST) IgE serum content. These data were then compared with results of analysis of soluble IL-2R levels.

*Assaying for Soluble Tac Protein*

Soluble Tac protein was measured using a double epitope "sandwich-enzyme-linked immunoassay," or ELISA. This ELISA employs two monoclonal antibodies binding at distinct epitopes on the Tac protein. The conversion of substrate to product is proportional to the amount of Tac protein present and the assay is made quantitative by comparison to a standard preparation of soluble Tac protein. The results are expressed as (U/mL). Age-matched normal control individuals were included in the study. Linear regression test was used for statistical analysis.

## RESULTS

Shown in Figure 1 are the results of IL-2R concentration detected in various groups of children with allergic disorders compared with normal controls. There was considerable overlap in the concentrations of soluble Tac protein between healthy children, patients with mild asthma, patients with mild eczema, patients with severe asthma, and patients with severe eczema (Fig 1). Although serum Tac peptide concentrations were slightly elevated in patients with severe eczema, no significant differences were observed between this group and healthy controls. Serum Tac concentrations were not significantly correlated

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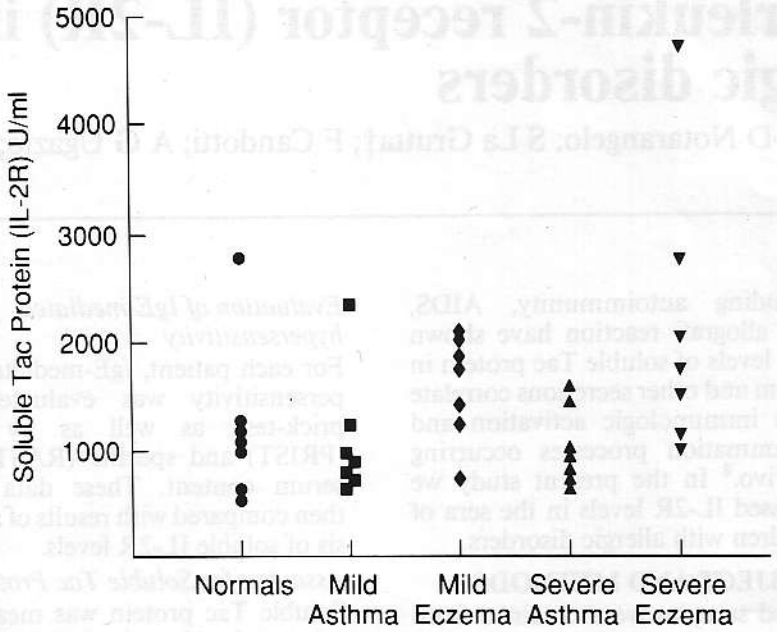


Figure 1. Serum levels of soluble interleukin-2 receptor in children with allergic disorders and in age-matched controls.

with serum IgE concentrations in any of the groups under study (Fig 2) IgE versus mild eczema: r = .232, $P = .617$; IgE versus severe eczema: r = .121, $P = .796$; IgE versus mild asthma: r = .379, $P = .401$; and IgE in severe asthma: r = .145, $P = .757$). Similarly, serum Tac concentrations were not significantly correlated with the skin-positivity as determined by prick-skin testing (Table 1).

## DISCUSSION

Elevated serum concentrations of soluble Tac-peptide (ie, of the soluble form of the $\alpha$-chain of IL-2 receptor) have been demonstrated in several conditions associated with immune activation and/or dysregulation, such as autoimmunity, AIDS, and allograft rejections and systemic sclerosis.[8, 11] It has been postulated that abnormalities of the immunoregulatory network may play a role in the pathogenesis of allergy.[12, 13] Indeed, decreased numbers of CD3 and CD8 circulating T lymphocytes, and reduced in vitro suppressor cell activity have been reported in patients with allergic disorders.[12, 14–16]

On the basis of these data, we have analyzed serum concentrations of soluble IL-2R in a cohort of 28 allergic children with atopic-eczema or asthma and seven age-matched healthy controls. Serum concentrations of soluble IL-2R were slightly elevated in children

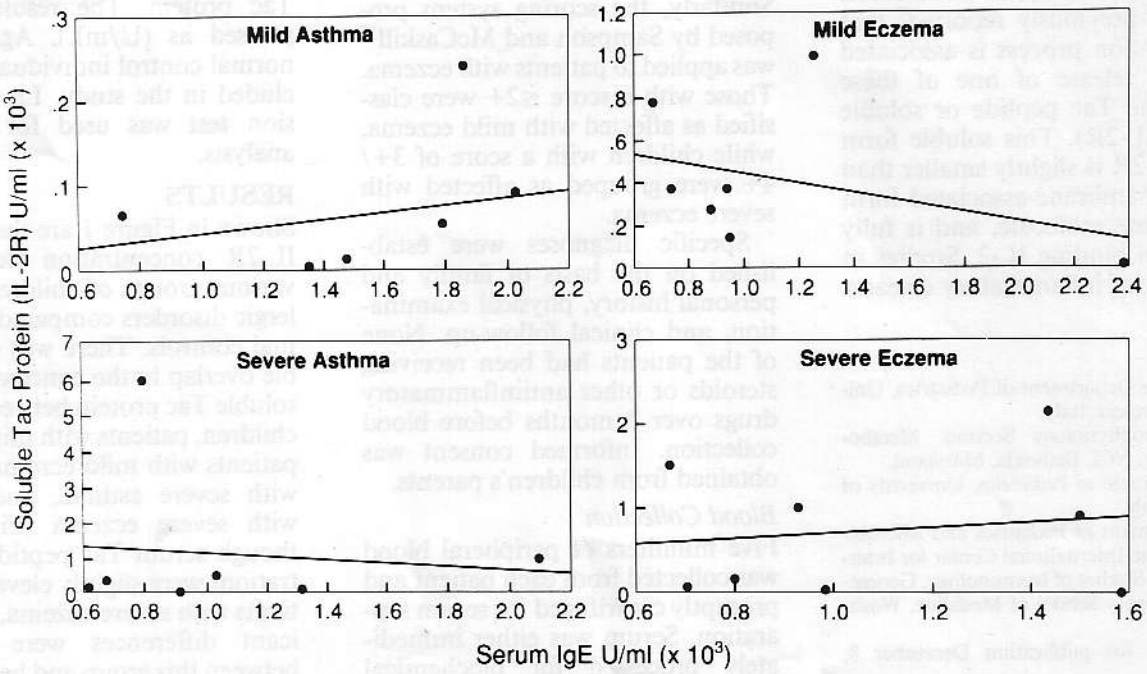


Figure 2. Correlation between serum levels of soluble interleukin-2 receptor and total IgE in children with allergic disorders. Linear regression test was applied in each group.

Table 1. Correlation of IL-2R Serum Levels and Skin Test Positivity

| | Asthma | | | | Eczema | | | |
|---|---|---|---|---|---|---|---|---|
| | Mild | | Severe | | Mild | | Severe | |
| | Skin Test+ | Skin Test− | Skin Test+ | Skin Test− | Skin Test+ | Skin Test− | Skin Test+ | Skin Test− |
| n* | 5 | 2 | 6 | 1 | 2 | 4 | 3 | 2 |
| $\bar{X}$† | 1177 | 966 | 1018 | 982 | 1299 | 1654 | 1445 | 2288 |

* n = number of subjects tested.
† $\bar{X}$ = geometric mean serum IL-2R concentrations (U/mL).

with severe eczema; however, the difference was not statistically significant as compared with healthy controls.

Interestingly, Matsumoto et al have recently reported elevated serum levels of soluble IL-2R in children with eczema or food anaphylaxis.[5, 17] In both the study of Matsumoto et al and in the present study, similar assays were employed for measurement of serum concentrations of soluble IL-2R. Although statistically significant results were obtained only in the study of Matsumoto et al, in both studies an overlap between serum concentrations of soluble Tac protein in children with eczema and age-matched controls was clearly observed. Assessment of serum Tac concentrations is therefore of questionable usefulness and significance for monitoring allergic inflammation in this group of patients.

Controversial results have been reported on serum soluble IL-2R levels in patients with asthma. Brown et al reported increased levels in asthmatic subjects, independent of severity of the disease and of the presence of acute symptoms.[18] Corrigan and Kay reported higher serum levels of sIL-2R and IFN gamma in adults with acute asthma.[19] In contrast, more recently, Matsumoto et al have reported that serum levels of sIL-2R are not increased in children with asthma. These apparent discrepancies may reflect cellular release of cytokine during in vitro clotting procedure, thus affecting serum cytokine levels. In order to avoid this problem, we have immediately processed each blood sample for serum separation.

Our results on serum IL-2R levels in asthmatic children are in keeping with the observations by Matsumoto et al and support the notion that differences in the severity of allergic reactions do not appear to result in systemic amplification of the immunologic activation, as suggested by the lack of correlation of soluble IL-2R concentrations in allergic children with total IgE RAST or prick skin test positivity.

The results of the present study are in agreement with previous observations demonstrating that serum IL-2R concentrations are within the normal range in children with bronchial asthma and extremely high total IgE levels.[5] Immune activation mechanisms involved in IgE synthesis and in the production of soluble IL-2R appear to be different. Hawrylko et al have recently reported increased cellular production of cytokines during inflammatory processes.[20] Thus, evaluation of cytokine production by mononuclear cells might represent a better inflammatory index than serum cytokine levels.

In conclusion, while it is possible that abnormalities of other immunoregulatory pathways (including IL-4, gamma-IFN, IgE-binding factor) are associated with allergy[21–24] (and their measurement may thus be useful in monitoring of these patients), our data suggest that evaluation of serum soluble IL-2R levels is of limited value in the assessment of allergic children, with the possible exception of patients with severe eczema.

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