

Reduced plasma c-AMP levels in children with atopic dermatitis

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Plasma levels of cAMP and serum concentrations of IgE have been determined in children with acute atopic dermatitis (AD) and in a healthy control group, to illuminate the pathophysiological mechanisms that cause AD.

There were significantly lower plasma levels of cAMP ($P < 0.001$) and significantly higher levels of serum IgE ($P < 0.004$) in children with AD, in comparison with a healthy control group. It is possible that defective control of c-AMP levels could contribute to the immunopathogenesis of AD and monitoring levels may be of value in the clinical evaluation of the disease.

**Damiano Carmelo Salpietro¹,
Francesco Naccari²,
Isabella Polimeni³,
Cristina Pellegrino²**

¹Chair of Pediatric Therapy, Institute of Medicine Preventive and Social Pediatrics, ²Chair of Veterinary Pharmacology, Department of Medicine and Veterinary Pharmacology, ³Fellowship – University of Messina (Italy)

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Prof. Damiano Carmelo Salpietro, Istituto di Medicina Preventiva e Sociale Pediatrica – Servizio di Genetica Medica – Policlinico Universitario, Via Consolare Valeria – Gazzi, 98100 Messina, Italy
Tel: +39-90/2213114
Fax: +39-90/2213101

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Atopic dermatitis (AD) occurs in 5–6% of pediatric patients. In spite of the numerous recent discoveries, the pathogenetic mechanisms responsible for AD aren't completely explained.

Research carried out in the last few years has shown (1) that AD, as one of the atopic diseases, has a genetic component. Many studies have shown linkage between atopy and a cluster of genes located on chromosome 5, site q13, that control specific cytokine production (IL-4, IL-13, IL-3, IL-5, IL-9). These could favour a predominance of Th-2 over Th-1 lymphocytes and lead to the production of IgE (1, 2, 3).

Studies of AD have demonstrated numerous immunologic alterations: dysregulation of monocytes and T cells (4), increase of IL-6 (5), overexpression of IL-10 (6) and some alterations of c-AMP generation (7, 8, 9). It has been suggested that the immunopathology of AD could be related to an altered cellular response, caused by an increase of the phosphodiesterase (PDE) enzyme, that leads to an increased degradation of the second messenger c-AMP. This decrease of c-AMP could be responsible for defective intracellular regulation of monocyte functions, leading to altered immunological activity and cutaneous inflammation (10).

In studies carried out on newborns at increased atopic risk (10, 11), we showed an increase of the serum IgE and a decrease of the urinary c-AMP levels. These results lead us to believe that there is a "genetic" deficit in the synthesis of c-AMP and/or a change in the phosphodiesterase synthesis (11, 12).

The aim of this research has been to evaluate the plasma levels of c-AMP and the serum concentrations of IgE in children affected with AD in an acute phase, to give a further contribution to the understanding of the pathophysiological mechanisms responsible for the induction of AD.

Materials and methods

The studies have been carried out on 30 children (18 male and 12 female), affected with acute atopic dermatitis and subjected to no pharmacological and/or dietary treatment, and on 30 healthy children (17 male and 13 female), with both groups of children aged between 3 and 36 months.

For the evaluation of the plasma c-AMP levels and of serum IgE concentrations, blood samples were taken and collected in glass tubes. After centrifugation all the plasma samples were stored in a freezer at -20°C until testing.

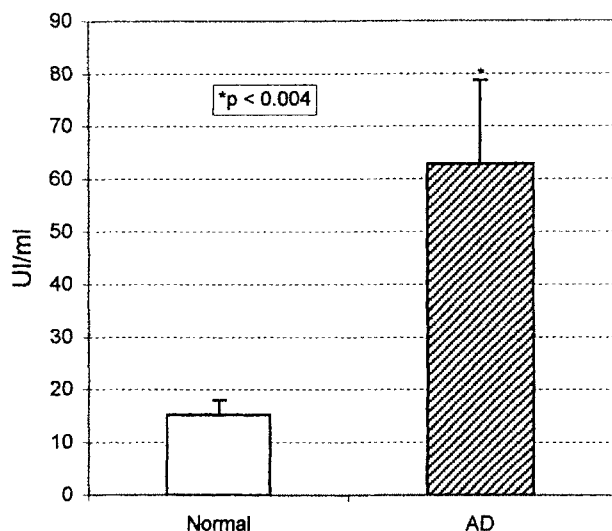


Fig. 1. Plasma levels of IgE (Mean values $\pm$ SE) in normal and atopic children.

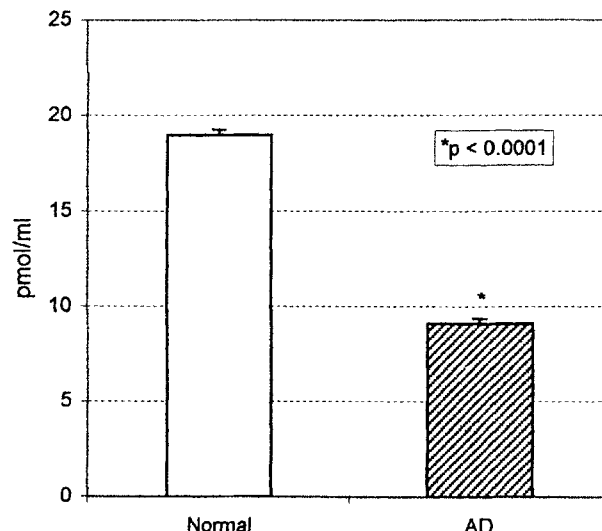


Fig. 2. Plasma levels of c-AMP (Mean values $\pm$ SE) in normal and atopic children.

The diagnosis of AD was made according to new allergological diagnostic principles (13, 14, 15). The allergens used (supplied from LOFARMA, Milan) were: casein, lactalbumin, betalactoglobulin, egg albumen, *Dermatophagoides farinae* and *D. pteronissinus*, as well as the positive (histamine) and negative (physiological solution) controls. For subjects more than 12 months old, pellitory, olive, mix of gramineae, dog hair, cat hair, fish, chocolate, tomato, peach and apple have been also used. Evaluation of cutaneous reactivity has been made according to the guidelines of the Italian Allergy and Clinic Immunology Society.

IgE serum concentrations were measured by radioimmunoassay (RIA).

The c-AMP content in the plasma samples was evaluated with RIA method, using the RIANENtm c-AMP*¹²⁵ kit. This method uses the competition between a known quantity of standard antigen and of a plasma sample, in the fixation of a determined share of the specific antibody. The antigen-antibody interaction has been expressed by a standard curve; the unmarked quantity of antigen in the sample has been determined by means of interpolation.

The statistical analysis of the results has been carried out by the software program ANOVA CLR for the evaluation of student t-test and by the software program SPSS to estimate the Spearman rank correlation coefficient between AD and a healthy control group.

Results

The IgE serum levels were significantly higher ($P < 0.004$) in children with AD (62.8 ± 15.89 UI/ml), in

comparison with healthy controls (15.28 ± 2.73 UI/ml), (Fig. 1).

Evaluation of individual IgE values showed that in relation to age 23/30 (77%) of the children with AD were above normal, while 30/30 (100%) of the healthy subjects were within the normal range.

The SPT was positive to milk proteins in 18 children with AD and in none of the healthy children. Moreover, the prick was positive in another 2 subjects with AD (1 for tomato, peach, milk proteins, *D. pteronissinus* and *D. farinae*; 1 for fish, apple and pellitory). The RAST was positive class 3 (20–100 SU/ml), 4 (100–300 SU/ml) or 5 (> 300 SU/ml) in 15/30 (50%) of the subjects with AD (13 for cow's milk proteins and 2 for egg albumen) and in none of the healthy subjects.

The plasma levels of c-AMP were significantly lower ($P < 0.0001$) in children with AD (mean values 9.11 ± 1.42 pmol/ml; range of variability 7.11–11.5) in comparison with the controls (mean values 18.97 ± 1.61 pmol/ml; range of variability 16.3–21.4 pmol/ml) (Fig. 2).

There was no correlation between IgE concentration and c-AMP levels in either the control or AD group.

Discussion

The significantly lower c-AMP plasma levels in children with acute AD in comparison with the controls, agrees with the decrease of the nucleotide documented by other researchers in monocyte cultures (7, 10, 16).

The low levels of c-AMP could be the expression of a basic defect in synthesis and/or of overproduc-

tion of phosphodiesterase (PDE), which is the enzyme responsible for c-AMP degradation.

The low levels of c-AMP could have an important role in both initiating and maintaining the immunopathology in AD children. In fact, as hypothesized by other researchers, the reduction of c-AMP would cause an increase in prostaglandins E₂ (PGE₂) and in interleukin-10 (IL-10), in monocytes and, probably, also in the Langerhans cells. This could favour the switch of the TH0 lymphocytes toward a TH2 rather than a TH1 phenotype (8). This would cause a reduction of IFN- γ and an increase in IL-4 and IL-5 production that leads, as final result, to an increase in IgE (4, 7, 16).

Others have shown that AD is characterized by an increased histamine release from basophil granulocytes, an increased IgE production and a decreased intracellular response to c-AMP (16, 17, 18).

Drugs, which interfere with c-AMP production or degradation, could have an important role in shifting the immunologic balance toward a TH1 rather than TH2 lymphocyte phenotype. In fact, a substantial reduction of PDE has been shown in patients with severe AD, after 12 weeks of therapy using recombinant IFN- γ (7).

Our studies are still in progress to evaluate the c-AMP levels in a larger number of AD children, after prescription of pharmacological and dietary therapies.

If these results are confirmed, the measurement of the plasma levels of c-AMP could represent another useful parameter for the screening of the subjects with AD, and for the dynamic evaluation of response to therapy.

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