Theses of Ph. D. dissertation

Clinical and laboratory investigations in case of children suffering from atopic eczema/dermatitis syndrome and living in Borsod-Abaúj-Zemplén County

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Introduction: The prevalence of atopic eczema/dermatitis syndrome (AEDS) is increasing worldwide. Genetic, other endogenous and environmental circumstances also play an important role in this disease's remaining a serious one and thus in creating a multifactorial clinical picture of it. Among the essential ones are those skin physiologic changes that are genetically determined. The most important of them all is: the damaged hidrolipid layer with its damage caused by the decreased ceramid content, this effect further strengthened by the sphingomyelin deacilase deficiency. The pathological barrier function generates and appropriates the effectiveness of potential antigens and the strengthening of other biologically, physically, and chemically damaging factors. Out of the biological factors, the Staphylococcus aureus has a special relation to the atopic skin. Depending on the mode and/or place of taking samples, and on the actual seriousness of the inflammation of the skin, in 56-90% of the patients suffering from the disease, the bacteria can be detected in magnitudes higher number compared to those not suffering from atopic skin disease. The colonization and its forming on the atopic skin are supported by the fibrinogen and fibronectin binding proteins which are generated by the high levels of interleukin–4 and by the low values of beta defensine levels. There are many ways in which colonization may lead to the progression of atopic skin process. Invasive pyogenic skin infection may come into being. The lack or shortage of ceramid is further aggravated by the Staphylococci as they decompose the ceramid in the lipid layer of the skin.

The staphylococcal exotoxins, (enterotoxin A, B, toxic shock syndrome toxin etc.) that result in thousands of times stronger immune reactions than the ordinary antigens and also act as superantigenes (SA) are produced by half of the colonizing bacteria. They intensify -in many points- the inflammation process in the patient's body suffering from AEDS. In the peripheral blood, the Th2 limphocyte dominates. In the acute period in the skin Th2, in the chronic one the Th1–type cytokines play the dominating role. It is the inflammatory epidermal dendrite cells that bring about the changes. The Langerhans cells, monocytes and particularly the inflammatory epidermal dendritic cells, significantly advance the antigen presenting process. The expression of CD86 on the surface of Langerhans cells, the appearance of B 7.2 costimulatory factor on the B cells, and the CD28 connection on the surface of Th2 cells are necessary for the full activation of T-cells (antigen presenting cell–MHC peptide–TCR connection) and for the production of IgE. The reduced apoptosis of the T–memory cells and eosinophils and the increased apoptosis of the keratinocytes also play an important role in the pathomechanisms of AEDS. Based on recent researches, some authors even suggest the possibility of autoimmune processes. The root of their assumption is that they could detect some IgE–type antibodies–the ones that react to the structural proteins and to some epithelial structures from the serum of some patients suffering from acute

AEDS. The presence of anti–sweat IgE antibodies in the sweat at itself is also possible. The majority of patients do not only suffer-during their lives–from one atopic disease effecting solely one body organ but suffer from more. As the disease unfolds, the first complaints are usually skin or gastrointestinal symptoms. Dermatitis often develops in babyhood. Its process is characterised as a chronic relapsing one. The skin–process–in part of the cases–slows down or stops before adolescence. As it is a multi-factorial syndrome, the therapy varies, too. The restoration of the barrier function of skin with the appropriate bathing and skin hydrating balms and lotions is essential.

For the anti–inflammatory and skin– softening treatment of the involved patches, the following materials and medicines are recommended: tar, glucocorticoids, salicylate, urea and antimicrobic stuffs on the sick spot. We have had good results with immunsupressive macrolid–containing ointments. For longer periods of use–per orally–the sedative or non-sedative forms of antihistamines can be chosen or the same but intermittently although the medical literature is quite split over this question. The use of proper antibiotics is also suggested in cases when the Staphylococcus aureus colonization causes a persistently acute syndrome that is close to or steadily becoming erythrodermia. Besides this, the antibacterial and corticosteroid mixture can also be applied on the spot. If there is a case in which the sensibility to inhalant or to nutritive allergens is clearly detected, an effort should be made to eliminate the above allergens. The specific immune therapy does not necessarily indicate the allergy that only manifests itself in dermatitis symptoms. The climatic treatment eliminates the allergens and is also useful to change the patient's psychic state for the better. In cases when it seems necessary, psychotherapy may also be applied, and informing and educating the other members of the family is also important. In children's cases, the application of systemic steroid can only be allowed in exceptional cases, and for a short period of time. Chinese herbal mixture–because of their immune suppressive effect–can also complement and add to the traditional healing methods. The basic immunologic differences and the symptoms can be influenced in some other different ways, as well. The local (UVA, UVB, UVA+B photo therapy, local immune suppressive macrolids) or systemic immune modulation are sufficient methods for that. The systemic dosing of Cyclosporin–A can be applied in cases when there is no reaction to other therapies. There are also experiments with dosing anti–IgE, anti– IL–5, gamma interferon intravenous immunglobulin, or even with dosing the patient's own blood.

Main aims

I started to deal with patients who came to see me and suffered from atopic eczema/dermatitis syndrome in 1991, in the county of Borsod–Abaúj–Zemplén. During my duty my purpose was and has been to collect data of these patients, to examine, to assess my findings, the peculiarities of my research and to sum up the results of my collaborative work.

My endeavour is to answer the following questions:

1. Can the barrier dysfunction – that characterises the disease – play any role in the developing of atopic skin process and in the progression of atopic eczema/dermatitis syndrome? If yes, what kind of role?
2. Can any differences be detected with immune laboratory tests among patients suffering from atopic eczema/dermatitis syndrome differences that can be considered as new and what influence can they have on the overall clinical picture?
3. What kind of new therapeutic methods and types of medicine can be applied in Hungary to treat children suffering from atopic eczema/dermatitis syndrome?

The tests and experiments to answer the above questions (divided into the relevant topics)

I. The occurrence of atopic eczema/dermatitis syndrome in the village of Bükkszentkereszt and Répáshuta among babies born between 1983-2002. The comparison of their 1992-1994 data to the data of babies born at the same period in the village of Szirmabesenyõ.

Patients

Bükkszentkereszt and Répáshuta are two quite enclosed communities of Bükk Mountains, about 30-40 km from Miskolc. Szirmabesenyõ lies only 3 km from the industrial areas of Miskolc. During my study work I attended to the data of all the children who were born in the period of time in question (July, 1983 to June 1984, January, 1992 to December 2002). I also carried out the comparative analysis of the 56 babies born in the 3–years–period in Bükkszentkereszt and Répáshuta between 1992 and 1994 compared their data with those of the 178 babies born in Szirmabesenyõ at the same period.

Methods

I saw the children when I went to their villages, organised by the Mobile Health Specialists' Service. I recorded the data characterising the state of the skin, enteral and respiratory symptoms. Up to the babies' first birthdays I saw the children and examined them minimum 5 times, after that– up to their 6th birthday –I examined them minimum 4 times a year, in person. As to the 21 children born in 1983-1984, I only took their medical history records into account. I personally examined a few of them after the age of 8, but I still personally keep up with examining the children born after 1998. As the length of time when the children were examined varies depending on their date of birth, I only took into account–during the statistical analysis–the AEDS cases that had developed fully before the children's first birthday. In most cases–however–the atopic skin process had taken shape by that time.

Results

In the village isolated from the industrial region – Bükkszentkereszt and Répáshuta–where no population fluctuation is shown, 199 children were born in the tested period. Of them, 69 showed AEDS symptoms before their first birthday. After the analysis observing their data divided by the year-I came to the conclusion that there was no statistically significant change in the occurrence of the disease.

Carrying out our survey based on the years 1992 to 1994, I found that the AEDS occurrence showed higher values in case of the children born in Bükkszentkereszt and Répáshuta, than in Szirmabesenyõ–which is in an industrial region at the foot of Bükk Mountains. 56 children were born in Répáshuta and Bükkszentkereszt between 1992 and 1994. Out of them AEDS developed before the age of one in 21 cases (37.5%). During the same period in Szirmabesenyõ 30 children developed AEDS by the age of one (16.8%). The difference is statistically significant: p=0.0026 Odds ratio: 2.96. The comparative surveys concerning the others years have not been completed yet.

Conclusion

Because of the small number of the samples used in the statistical observations, no serious epidemiologic consequences can be stated. My data suggest that in the two enclosed villages, a kind of population came into being–at random–in which the occurrence of AEDS is higher. At the same time it is remarkable that here the occurrence doesn't seem to change, it shows constant values. In Szirmabesenyõ -which shows closer values to the nationwide average- the changes in the number of occurrence can only be processed as numeric data in two years' time.

II. The examination of data characterising the process of atopic eczema/dermatitis among the children whom I saw as patients

Patients

I have details of 713 children altogether concerning the process of AEDS. The collection of data took place focusing on the skin process on the other side effects usually accompanying other atopic diseases, on the forming of allergic sensibility and also on the atopic family history. The patients are being treated–at present–at the Borsod–Abaúj–Zemplén County University Hospital's Institute of Child Health. There were a minimum of 113 children who have been under surveillance up to the age of 5 and the further 100 children under surveillance up to the age of 10 and the seriousness of their case can be described as that of average or medium serious. The seriousness of the state of the dermatitis among the 500 children under surveillance up to the age of 14 shows inhomogeneous details.

Methods

The details in the children's medical treatment records concerning the process of their atopic skin process, allergic sensibility and other accompanying atopic diseases derive from my own comments during the healing process. During the statistical analysis I applied the following methods: "Student–t" test, Fisher exact test, Chi2 probe–test, "Odds" ration calculations, "Yates" correction, and GraphPad Software V.2.03 version.

Results

Family history

Based on the analysis of children suffering from AEDS but regularly checked, I got the following results concerning the process of the disease: analysing the family history, I found the occurrence of eczema 36.5%, but at the same time the occurrence of asthma and rhinitis was 14.4% and 15.3% in the families observed. The occurrence of atopic diseases was 28.4% observing the maternal lineage, 19.8% observing the paternal lineage and 20.3% in case of that of siblings. These details correlate with the results of other studies.

The forming of the skin process

The appearance of skin symptoms on children suffering from atopic eczema/dermatitis syndrome: In case of the children under surveillance up to the age of 6, and treated in our institute (263 children), the appearence of sign the disease was 93.8% before the age of 3, 74.8% before the age of 1, 43.3% before they were three months old. Out of the 192 cases followed up to the age of 10, AEDS developed in 10 cases between the age of 6 and 10. It is 5.2%. Out of the 100 children with their cases followed up to the age of 14, 2 showed their symptoms first between the age of 10 and 14. The results clearly indicate that in most cases the AEDS skin process developed already in babyhood.

The presence of Specific IgE positivity and atopic mucous membrane signs in cases of children of different age suffering from serious atopic eczema/dermatitis syndrome

We examined the allergic sensibility with Specific IgE detection on 100 children suffering from serious AEDS–divided into three age–groups. The results indicate that the IgE psitivity shows minimal changes after the age of 10 in this group with serious skin symptoms. The accompanying mucous membrane symptoms–on the other hand–manifest themselves mainly after that age.

The beginning of mucous membrane symptoms, in medium serious atopic eczema/dermatitis cases, the results of skin prick tests and allergen–specific IgE examinations in different age–groups.

We examined the allergic sensibility with skin prick test, and specific IgE definition on the 200 children divided into two age–groups, with their cases being medium serious. The prick test positivity in both groups was significantly higher than the specific IgE positivity. Under the age of six, 42 cases out of 74 (56.7%) prick examinations showed positive results, and in 29 cases out of 81 the specific IgE tests were positive (35.8%) ($p=0.0102$, Odds ratio: 2.353). Including the children over 6,92 prick tests out of 145 were positive (63.4%) and 41 IgE tests out of 116 (35.3%, $p< 0.0001$, Odds ratio: 3.175). In cases of babies and patients continuously showing skin symptoms, the prick test cannot be carried out; the only allergen research method is the specific IgE examination. In the not so serious cases, the prick test should be taken in the periods when there are no symptoms shown, as it shows significantly higher and more frequent positive results.

Other atopic symptoms, accompanying the atopic eczema/dermatitis syndrome, remaining until the age of 14

To decide how often the AEDS still taking place at the age of 14 is accompanied with mucous membrane symptoms, we analysed the data of 500 children suffering from AEDS over 14 with their skin symptoms showing heterogeneous seriousness. Among them the occurrence of mucous membrane symptoms was 40.6% (203/500). Among them 123 suffered from asthma, 81 from rhinitis and 56 from conjunctivitis. In this group we did not assess the results of allergen research, because of the sparse information available. Comparing the characteristics of the three groups, it can be seen that–after the age of ten–mucous membrane symptoms more often accompany the more serious skin process than in case of the less serious ones. These results are very similar to those in the medical literature, already well–known. With presenting them, my aim was to describe my patients.

III. The analysis of the occurrence of cataract developing as an accompanying complication of atopic eczema/dermatitis syndrome in case of treated children suffering continuously from skin symptoms. HLA examinations in order to get information on the genetic background

Patients

Among the children regularly visiting the surgeries of our dermatological institute (and diagnosed as children suffering continuously from AEDS according to the Hanifin & Rajka's criteria), 612 youngsters were directly checked by an eye– specialist between the 15th December 1993 and the 30th July 2004. Their age at the time of examination was between 1.1 and 17 (5.2 on the average). The skin process had already been in effect for 2.2 years on the average (0.6 – 10). The control group is the other 10.482 patients seen at the eye–specialist's surgery of the institute–at random–between the age of two–month-old and 14 – year –old.

We also genetically examined 24 out of the 25 patients with AEDS also suffering from cataract and 11 children with AEDS but not suffering from cataract. We defined the HLA antigens of the 35 sick children, and those of the 913 healthy Hungarian control persons.

Methods

The eye examinations took place at the Eye Specialists' Unit of the of Borsod–Abaúj–Zemplén County University Hospital and at the Ortoptical surgeries.

The genetic tests were carried out at the Moleculargenetic Laboratory of the National Haematological and Immunologic Institute. The HLA–ABC definition was accomplished with serologic methods, where as the DRB 1, DQB 1 alleles were defined with molecular–genetic (PCR) methods. The results were compared to the details of 913 healthy blood donors.

Results

The cataract and keratoaconus are the minor diagnostic criteria of AEDS. I was interested in the occurrence of alterations among my patients. We were looking for keratoconus and cataract as minor diagnostic signs among the 612 AEDS patients (301= 49.1% girls and 311= 50.9% boys) suffering seriously or medium – seriously from the disease. Cataract showed 4.08% frequency (25/612). Among the 10482 controls–children only 11 suffered from congenital cataract (0.104%). At this age, AEDS was never accompanied by keratoconus. Cataract was detected on 28 eyes of the 25 patients seen. The average age of the children suffering from eye lens dimness was 7.9 (between 4 and 16.5) at the time of the first "positive" diagnosed examination. The skin process had been in

effect for 5.8 years on the average (between 0.5 and 14.5 years). Seven of them even suffer from asthma. Their SCORAD Index was calculated at the time of diagnose as 51 on the average (36 to 91). In the eye–lenses found dim earlier, we did not detect any progression, whereas, in case of two patients the dimness had cleared up during the period we had followed their cases (3 and 7 years). During the HLA examinations among the AEDS patients also suffering from cataract –compared to the rest of the population as normal– the frequency of certain alleles was different in that group. Compared to the rest of the population, the following alleles showed higher frequency: HLA-A3 (37.5% compared to 20.8%) B62 (15) (25 vs. 10.7%) B27 (18.8 vs. 10.1%)HLA-DR1 (37.5 vs. 18.8%) DR4 (31.2 vs. 17.9%) DQ1 (81.3 vs. 61%) DQ3 (81.3 vs. 56%). The occurred alleles with lower frequency: HLA B8 (4.1 vs. 21.5%) HLA-A1 (6.3 vs. 28.5%) A10 (6.3 vs.18.6%) B7 (6.3 vs. 16.6%) DR17 (3) (12.5 vs. 28.1%) DR7 (12.5 vs. 26.2%). Out of the 35 children (AEDS patients) undergone HLA examinations, 2 of them carry the B8 allele (5.7%). Compared to the controls, it is significantly lower (p= 0.0198, Odds quotient: 4.51). Among the AEDS patients also suffering from cataract the occurrence of HLA B8 is even lower (1/24, 4.1%).

Conclusion

The results imply that the frequency of HLA B8 allele in patients with AEDS and even in those with anterior subcapsular cataract is lower than in that in normal controls. We need more data for the correct analysis.

IV. The observation and examination of the moisture content of epidermis and its Na^+ and Cl^- concentration in the induced sweat in cases of atopic eczema/dermatitis syndrome

Patients

We carried out the comparative examination of the moisture content of the skin and the Na^+ and Cl^- content of sweat on 20 children suffering from AEDS and also on 20 healthy children aged 0 to 16. The average age of atopic patients was 6.3 year-old (12 boys, 11 girls) while that of the controls was 7.2 year-old (11 boys, 9 girls).

Methods

The definition of the moisture content of skin happened with SCALAR MY–707 moisture checker appliance (corneometer). From September to April I measured the moisture content of skin on the cheeks and on the skin surface of the arms inside the elbows where flexing them. The device displayed the results in percentages. The induction and the collection of sweat from the above mentioned parts of the elbow took place with iontophoresis with the use of SS–023 Pilogel disc. Macroduct Sweat Collecting System (3700 SYS Webster) was used. The measuring of Na^+ and Cl^- content of sweat was carried out with Wescor 3100 sweat–monitoring appliance. The display indicated the results in mmol/litre.

Results

The skin physiological parameters–we got on the atopic and on the control patients' skin-showed differences. We found the facial (21.1% vs.34.8%, $p< 0.05$), and brachial (28.5% vs. 34.3% $p< 0.05$) epidermal moisture–content significantly lower than in the controls. This is in accordance with the relevant literature.

The Na^+ and Cl^- concentration at the AEDS children patients was 37, at the controls it was 31 mmol/l on the average. The difference proved to be statistically significant ($p<= 0.05$). Besides this, at the controls we could always induce sweat whereas in case of the AEDS patients 3 attempts were

unsuccessful. As to the quantity of perspiration induced, the publications are contradictory. There are no details about the Na^+ and Cl^- content examinations of atopic patients' sweat in the scientific literature. Our findings might be the indirect signs of reduced sweat production in atopic dermatitis. Besides the structural and pharmacological differences of the skin, the effect of the anti–sweat antigens can also explain the above situation. The results of the skin physiological examination further strengthen the necessity and importance of barrier function improving treatments in the AEDS cases.

V. The examination of differences deriving from the skin barrier dysfunction in atopic eczema/dermatitis syndrome

Patients

We treated 7400 children (0-18 years of age) with skin related complaints between 01st January 1985 and the 30th April 1993. Out of them we diagnosed 675 pyodermic cases (9.1%), with 218 of them suffering from AEDS (31.4%). For comparison we had the details of 162 patients (0-18 years of age), seen in the year of 2000, also suffering from pyoderma.

During the examinations concerning the Staphylococcus aureus colonisation and the relation between the non-allergen specific antibodies and clinical state, we processed the data of 72 AEDS patients (aged 2-17, average age: 8; 34 boys, 38 girls) seriously or medium-seriously suffering from the disease. The control group consisted of 22 healthy children, aged 1.5-14 (10 boys, 12 girls, average age 8.6)

Methods

During my research into the pyogenic superinfection of atopic skin, I studied and searched through the medical and treatment records, diaries, and case history sheets in a retrospective way, I systematically sorted the data dividing them into aspects like: basic disease, age, pathogenicy, sensibility to antibiotics, seasonal occurrence, and therapy.

The samples for the microbiological examinations took place from the skin (showing the symptoms) with sterile cotton-wool-tampon in department of Paediatric Dermatology. The breeding of the culture was completed on solid culture medium (breeding ground)-for identification-with biochemical and other reactions, at the Bacteriologic Laboratory of the Municipal Health Authority of Borsod-Abaúj-Zemplén County. The resistance tests were carried out with disc-diffusion method. The definition of germ quantity/number happened with semi-quantitative method.

The identification of ANF antibodies took place with indirect immune fluorescent method on HEp2 cells, and I accomplished the measuring of anticardiolipin and anti â2 glycoprotein I with ELISA method at the Regional Immunologic Laboratory of the DEOEC IIIth Internal Medicine Clinic. To examine the total IgE content of the serum, we applied "immunoblot" test (INTEX, Basel).

Results

The occurrence of bacterial skin infection in atopic eczema/dermatitis syndrome

I analysed the result of microbiological tests on the secretion samples from wounds of pyodermic patients to help me select-later-the therapy without knowing the sensibility to antibiotics. Among the analysed pyodermic cases, the most frequent occurrences were the primer impetigo and the superinfection of atopic skin: 218/675 cases (31.4%). In 494 cases the bacteriological tests showed positive results. Out of the 162 pyodermic-positive bacteriological results in 2000, 39 were those of

atopic skin patients' (39/162→24.5%). The frequency of occurrence of the bacteria bred from skin was characterised by the predominance of Staphylococcus aureus and Streptococcus pyogenes. The two microbes were often at present together. The Staphylococcus aureus more often grew on atopic infected skin than on the non-atopic infected one. Among the atopic patients, the detection of Staphylococcus from wound mucous showed a statistically not significant rise from 74.2% to 87.18% by the year of 2000. The mixed-type of infections became more frequent (21.9% vs. 30.77%) and also showed a more serious clinical process.

Bacteria bred from the children's skin suffering from atopic eczema/dermatitis (colonisation and/or infection)

Here I was interested in the extent of the great amount of Staphylococcus aureus colonisation (so typical of AEDS, also well-known from scientific literature) and I also delved into the effect it had on my AEDS patients' laboratory and clinical parameters. Among seriously or medium-seriously suffering AEDS children patients, (SCORAD Index: 24-90, average: 48.3, average age:8) we found the percentage of the colonisation of the affected skin 41/72 (57%). It was Staphylococcus aureus in almost every case (40/41), but in three cases it was Streptococcus pyogenes-and in two cases both-from the samples taken from the skin surface. Clinically it showed pyoderma in 5 cases. The three Streptococcus pyogenes–positive patients were among them. The Staphylococcus aureus colonisation-with its typical occurrence of over 90% among the patients-showed lower figures when the AEDS patients belonged to an older age-group, according to the methods we applied, with 12% of the colonised ones showing pyoderma.

The occurrence of non-*allergen* specific antibodies in children's atopic eczema/dermatitis syndrome

The occurrence of non-allergen specific IgG and IgM antibodies was tested on the 72 patients. The higher amount of anticardiolipin IgM 12, IgG 2, anti ß2 glycoprotein I IgM 6, IgG3 and ANF could be detected in the cases of 10 children. The pathologically higher levels of the two antphospholipid antibodies occurred significantly more frequently with AEDS patients (18/72, 25%) than at the controls (1/22, p= 0.0378). The Odds ratio was 7, showing that the antiphospholopid (mainly anticardiolipin IgM) antibodies and their increase was seven times more frequent among AEDS-patients than those among healthy people. Th occurrence of ANF positivity (10/72,14%) was more frequent among the AEDS patients than among the healthy controls (2/22) but it is statistically not significant.

The occurrence of non-*allergen* specific antibodies and total and *allergen*-specific IgE in the serum of children suffering from atopic eczema/dermatitis syndrome

Besides the non-allergen-specific antibodies, we also examined the occurrence of total and allergen-specific IgE, their relation to each other and their relation to the serum of children suffering from atopic eczema/dermatitis syndrome, and to the serum of the healthy control-children. The occurrence of non-allergen specific antibodies (11/31=35%) was significantly higher in the normal serum showing the total IgE –in case of AEDS patients than at the healthy controls (1/20,p= 0.0169, Odds ration: 10.45). In case of AEDS children-patients showing high total IgE in their serum (10/41=24%, vs.1/20, p=0.1579), this difference is not significant. The occurrence of high total IgE with AEDS-patients in their serum was 41/72=57%, the occurrence of specific IgE was 37/72=51%. Therefore, the non-allergen specific antibodies significantly more often accompany the total IgE of normal serum than the total IgE of increased serum.

The association of increased anticardiolipin, anti ß2 glycoprotein I, ANF antibodies and the total IgE of the serum, and allergen-specific IgE in case of some children suffering from atopic eczema/dermatitis syndrome

Out of the 13 patients showing high anticardiolipin levels (11 IgM, 1 IgG and IgM, 1 IgG isotipe) 8 showed high total IgE levels in their serum. Out of these 8 cases, 6 showed specific IgE positivity. In two cases, the specific IgE could be detected paralelly with the normal total IgE. Out of the 8 patients, 5 showed specific IgE positivity only to inhalant allergen and 3 showed IgE positivity to both inhalant allergen and to endogenous allergen as well.

The types of allergens that can be detected besides the normal and increased serum anticardiolipin antibody levels in case of children suffering from atopic eczema/dermatitis syndrome

Out of the 13 patients that could be described as ones with high number of anticardiolipin antibodies, 6 produced mite specific IgE (Dermatophagoides Pteronissinus, Dermatophagoides Farinae), whereas out of the 59 normal patients with normal anticardiolipin levels only 10 produced this mite specific IgE. (Odds ratio 4.2, p= 0.0322). Therefore the mite sensibility significantly more often accompanies the cases of pathologically high anticardiolipin levels in the serum than in cases of normal anticardiolipin levels (in the serum). The weed-, and rye pollen specific IgE positivity also occurred more often with higher anticardiolipin levels, although no statistically significant difference was shown between the two groups. (Weed: 5/13, vs. 11/59, Odds ratio: 2.7, rye 6/13 vs. 18/59, Odds ratio: 1.95). These allergens are all of the inhalant type.

The occurrence of ANF, antiphospholipid and allergen specific antibodies on bacterially colonised and non-colonised skins of children suffering from atopic eczema/dermatitis syndrome

The occurrence of ANF, antiphospholipid and allergen specific IgE antibodies showed differences between colonised and non-colonised skins of children suffering from eczema/dermatitis syndrome. Examining the individual antibodies, this difference-that could be described with an average Odds ratio of 2.4-was not statistically significant. On the other hand, the total number of allergen specific IgE types (that could be detected) was significantly higher at the 20 patients with their non-colonised skins (36/17, p=0.0474, Odds ratio: 2.172). It is also to be mentioned that occurrence of rye pollen specific IgE was significantly more frequent among the colonised-skin patients (17/41) than among the non-colonised ones (7/31, p=0.0184, Odds ratio: 4.25). These findings suggest that the bacterial colonisation on the skins of AEDS patients facilitates the formation of polysensitization -mainly to the inhalant allergens.

The occurrence of bacterial colonisation of non-allergen specific and of allergen-specific antibodies at the 72 children suffering from atopic eczema/dermatitis syndrome with their SCORAD Index below and above the average

We examined the relation of the bacterial colonisation, ANF, antiphospholipid, allergen-specific IgE positivity compared to the SCORAD Index at children suffering from atopic eczema/dermatitis syndrome. The SCORAD Index on the average was 48.3 at the 72 AEDS children we saw. There was no significant difference between the bacterial colonisation data, (53.2), the ANF (52.9), the anticardiolipin (52.3), the antiphospholipid (anticardiolipin, anti ß2 glycoprotein I) (49.9), and between combined ANF and/or antiphospholipid (50.18) and the allergen specific IgE positivity that characterised the cases. On the other hand, the occurrence of higher-than-the-average SCORAD

Index was significantly more frequent among the patients showing bacterial colonisation than among the ones not showing that symptom (p= 0.0007, Odds quotient: 6.5). The occurrence of ANF positivity and of the specific IgE showed a minor-statistically not significant-correlation with the seriousness of the disease (Odds ratio: 2.22 and 1.603). The pathologically high levels of anticardiolipin antibodies did not usually show any relation to the SCORAD Index. However, the occurrence of the most serious AEDS cases (SCORAD>75) was significantly higher among the patients with high anticardiolipin levels (4/13) than among the patients with normal anticardiolipin levels (2/59). The Odds ratio is: 9.077, p= 0.0185. Taking the above results into consideration, we can come to the conclusion that the serious/pathological skin-process occurs more often among the patients with bacterially colonised skins than among the ones with their skins non-colonised.

VI. The effect of systematic-"immune-system influencing"-treatments on the general state of children suffering from atopic eczema/dermatitis syndrome

The effect of long-term Inosine Pranobex treatment-applied in pathologic childhood atopic eczema/dermatitis syndrome cases-on the clinical state of the children in comparison with the changes of the immune-parameters

Patients

During the examination period between May 1991 and July 1992 we treated 22 patients clinically seriously suffering from AEDS with Isoprinosine for half a year. The group consisted of 10 boys and 12 girls, their average age was 4.8, the youngest one being 1 year old, the oldest one 13.5. The control group was 20 AEDS patients who were not given Isopronosine, with their average age of 4.3 (ages between 1 and 14). It consisted of 9 boys and 11 girls. Among them we also tested-with half-a-year-time differences- we analysed those parameters that had shown significant changes among the treated patients. It took place between 1998 and 2000.

Methods

In the AEDS cases-during the testing period-the dosing of Inosine Pranobex varied. We divided the children into two age groups. In group I (children above 2) we gave 3*500mg in the first week, 2*500mg during the second and from the third week on: 500mg. The children under two got 2*500mg in the first week, 3*250mg during the second and from the third week on they got 500mg per day. (500-mg inosiplex/tablet, manufactured by BIOGAL Debrecen). We registered the typical characteristics of clinical and immunologic state of patients. During the examination period we analysed the frequency and length of the accompanying respiratory symptoms (rhinitis, asthmatic, infection) whereas as to the year before we leant on the parents' reports. The examination of the parameters of the immune system was carried out at the Central Clinical Laboratory of the Borsod-Abaúj-Zemplén County Hospital. In the time between, the clinical examination first took place 4 weeks later, then minimum after every eight weeks on a regular basis. The definition of the level of uric acid in the serum was carried out at the beginning and ending of the treatment. We clinically followed and tested the patients for 18 to 32 months until March 1994. To examine and to take into account the clinical changes with age, we used a control group of 20 children. Between 1998 and 2000, we-twice a year-carried out the examination of the parameters that had shown significant changes on the group of children consisting of 9 boys and 11 girls suffering from AEDS (aged 1-14, average age 4.3). They were not treated with Isoprinosine.

Results

During the prolonged immune modulative treatment (Inosine Pranobex), the children's clinical state undoubtedly improved. The accompanying respiratory symptoms (recurrent obstructive bronchitis in 6 cases, asthma in 3 cases, rhinitis allergic in one case and recurrent respiratory catarrhs in 2 cases) either got less frequent, mitigated/relieved or even came to an end, but remained the same in one asthmatic-rhinitis case. In 9 cases no respiratory symptoms accompanied the skin process. The oozing, and pimple eruptions disappeared from the skin, the itching sensation decreased, although did not stop. The percentage proportion of the infiltrated body surface significantly dropped from the average of 44.3 to 13.9 ($p<0.001$).

We found pathologically high total IgE levels in the serum in 14 cases. We did not detect-at this parameter-any changes until the end of the cure. The level of the average IgG rose statistically significantly from 9.154/l to 1156.6 g/l ($p<0.05$), the IgA levels from 0.93.8 to 1.85.0 g/l ($p<0.01$). These parameters did not show significant changes at the 20 control children-who was not given Isoprinosine-within half a year.

We found that the therapeutic effect was nice on the skin- and airway process of AEDS children, treated with Inosine Pranobex.

The changes in the clinical state of pathologically serious atopic eczema/dermatitis syndrome patients -treated with Cyclosporin-A-during the therapy and during the time we followed their cases

The patients

We applied Cy-A therapy in 6 cases when the seriously and long-time suffering AEDS children (4-16 years of age) were resistant to other therapies. Of them, two children are still being treated at the Immunological Unit of the Dermatological Clinic of DEOEC. Half of the patients are boys, half are girls. At the beginning of the therapy, their average age was 9.6 year-old (11.3 at the boys and 8.6 at the girls). The early onset of symptoms of polysensibility, high total IgE levels in the serum and in 5 cases positive atopic family history characterised the cases, apart from the case history, in all the cases.

Methods

We used Cy-A (Sandimmun Neoral, Novartis) in 6 cases for 12-85 weeks in cases when the children's atopic skin process-which was pathologically serious and had had its "ups and downs" from babyhood-did not react to any traditional therapy. The maximum daily dose was 3.5-5 mg/body weight kg. The clinical state of the patients during their under-surveillance period was registered with the definition of their SCORAD Index. We also regularly checked the blood pressure and the creatinin and Cy-A levels in the serum. (MEIA method, on AXIM measuring device).

Results

The average of the starting SCORAD Index of the patients who received Cyclosporin-A therapy was 70. At the end of the therapy it fell to 27. The short-term treatments showed temporary, the long-term ones showed long-lasting remission. We did not detect any serious side effects.

Conclusion

Among the AEDS children treated with Cyclosporin–A we could achieve temporary remission with short–term doses, and long–lasting remission by dosing the medicine according to therapeutic requirements at the beginning and by using smaller doses for a longer drawn period of time without serious side effects.

Summary

I began the examination and testing of the frequency of occurrence of atopic eczema/dermatitis in Bükkszentkereszt, Répáshuta and Szirmabesenyõ about 13 years ago. The final valuations of the current study will bee finished in the next two years.

The development of keratocunus is not typical among the children suffering from AEDS, based on the regular eye tests that we were the first to introduce nation wide in this age–group. The results imply that the frequency of HLA B8 allele in patients with AEDS and even in those with anterior subcapsular cataract is lower than in that in normal controls. We need more data for the correct analysis.

The answers to my questions, new findings and results:

1.A. The Na^+ and Cl^- ion concentration of the sweat induced from the atopic skins of children with significantly lower moisture content in their skin compared to non–atopic children's shows significantly higher values, than that of the control children. More often than not there is no sweat induced at all. *(New finding carried out by us).* These might be the signs of reduced sweat production in childhood AEDS.

1.B. The Staphylococcus aureus colonization, the dysfunction of the skin barrier helps the forming of polysensitisation in childhood AEDS. It was us who *first published* on "the polysensitisation facilitated by the bacteria" as *new observation in the scientific literature*.

2.A. The occurrence of antiphospholipid antibodies in childhood AEDS cases is significantly higher than that in case of the control children of the same age. This is especially outstanding at the group of patients with normal serum total IgE.

2.B. The increased anticardiolipin antibody levels are significantly more frequently accompanied by mite sensibility than in cases without that. *(New finding carried out by us).*

3.A. During the inosine pranobex treatment in childhood AEDS the serum IgA and IgG levels have risen. The mitigation and falling frequency of airway's infections, the atopic symptoms of airway and the decrease of microbial provoking factors may also have added to the improvement of AEDS children's clinical state.

3.B. Among the AEDS children treated with Cyclosporin–A we could achieve temporary remission with short–term doses, and long–lasting remission by dosing the medicine according to therapeutic requirements at the beginning and by using smaller doses for a longer drawn period of time without serious side effects.

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