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RESEARCH ARTICLE

Umbilical IgE and Advanced Glycation Products in Association with Allergies in Childhood

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Abstract: ***Background*:** Little is known regarding the possibility of predicting allergy in genetically susceptible individuals.

***Objective*:** We endeavored to measure the levels of IgE, IgA and advanced glycation end products (AGEs) in the umbilical blood of newborns of allergic parents.

***Method*:** We collected two groups of newborns, the first group of 20 subjects with non-atopic parents, and the second with 20 subjects with a history of allergy in one or both parents.

***Results*:** Neonates born to parents with allergies had increased levels of AGEs in their umbilical cord blood.

***Conclusion*:** This causes increased oxidative stress and an increased probability of allergy and asthma in a child ´s future. We therefore propose that such children should be followed with the aim of lowering AGEs and IgE throughout life.

Keywords: Advanced glycation end products, allergy, oxidative stress, immunoglobulin E, and umbilical blood.

INTRODUCTION

Free radicals are important factors involved in allergic reactions. These free radicals negatively influence the incidence and prognosis of allergy. Advanced glycation end-products (AGEs) activate receptors (RAGE) and cause long lasting inflammation, followed by free radical production. RAGE activate NF kappaB formation and activate intracellular oxidative stress. Furthermore they repress some endogenous autoregulatory functions leading to many diseases, including allergy [1]. Oxidative stress increases the inflammatory reaction in asthma and allergies. Supplementation with antioxidants decreases the inflammatory reaction in asthma and allergy, however these supplements do not prevent the formation of these diseases. To our knowledge, there are no published articles regarding AGEs responses, or the relationships between AGEs and IgE in newborns of allergic parents. We collected two groups of newborns, the first without allergy in parents (controls B) and the second with a history of allergy in one or both parents. The objective of this experiment was to test the levels of IgE, IgA and AGEs in umbilical blood in the two groups.

MATERIAL AND METHODS

The data collection took place from January to February 2015. 40 neonates were enrolled into the

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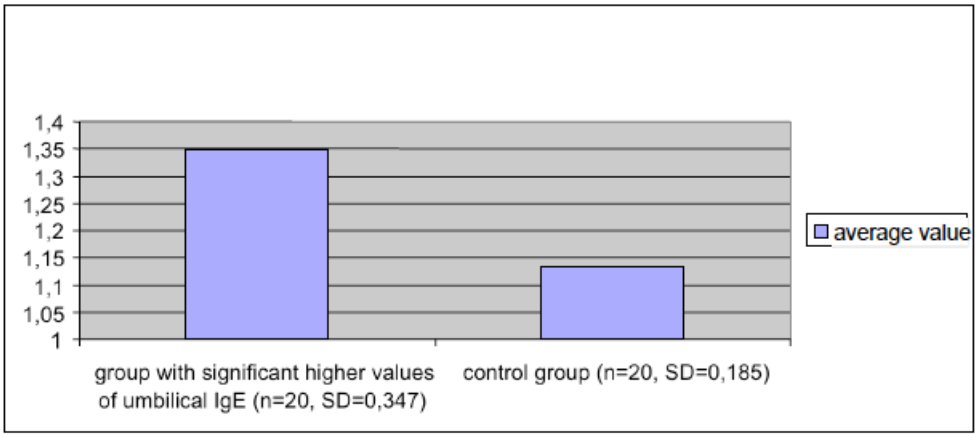

Fig. (1). Levels of advanced glycation end products in cord blood serum in newborns of allergic parents and controls. Results are expressed in fluorimetric units.

study and divided into two groups (A and B). Group A consisted of children born to parents with a positive history of allergy. Group B, the control group, consisted of children born to parents without allergies. Inclusion criteria for Group B children was low IgE measured at birth. IgA was measured in both groups to exclude the possibility of mixed maternal blood. In both groups we measured levels of IgE, IgA and AGEs. Glucose was measured in all mothers because high levels can negatively influence the levels of AGEs in umbilical blood.

BIOLOGICAL MATERIAL

AGEs were estimated fluorimetrically according to Henle (2) *et al.* (1999); in brief, sera samples were diluted 1:30 with phosphate buffered saline (PBS, pH 7.4), wavelength for excitation 370 nm, emission 440 nm, results were expressed in fluorimetric units (FU). Measurements were performed using a Cary Eclipse fluorimeter (Varian Australia Pty Ltd, 679 Springvale Rd., Mulgrave Victoria, Australia).

Umbilical cord blood collected without anticoagulant agents (at birth), venous blood collected without anticoagulant agents in the first and third year of life stability1 week at + 4 ± 8 °C, tests were performed always within 24 hours of collection.

Determinations of IgE up to the year 2010 was performed by ELISA kits f. RADIM, calibration range 0,4 -1000 IU/mL, from the year 2011 determinations are performed by chemiluminescent immunoassay kits on Total IgE Beckman Coulter, the immunoassay analyzer Access 2, calibration range 0,25–3000 IU/mL, expected reference values under 5 years less than 75 IU/mL.

Determination of IgA

Immunoturbidimetric determination of immunoglobulin A by kits IgA K-Assay IgG Beckman Coulter, on the analyzer AU 480 Beckman Coulter, calibration range 0,2-8 g/L expected reference values in children under 1 month of age 0,08-0,89 g/L. Newborn children do not have registrable IgA unless there is mixing of maternal blood.

Determination of IgG

Immunoturbidimetric determination of immunoglobulin G by kits IgG Beckman Coulter, on the analyzer AU 480 Beckman coulter, calibration range 0,004-30g/L, expected reference values in children under 1 month of age 2,2-11,2 g/L, up to 1 year of age 5,5-14,7 g/L.

Determination of Glucose

Estimation of glucose by the kit of ERBA LACHEMA with glucooxidase on the instrument Beckman Counter AU 480.

STATISTICAL ANALYSES

Data are presented as means±standard error (SD). The Wilcoxon test and the Spearman´s correlation analysis were performed for the statistical evaluation of the group data with SPSS software.

A probability value of less than 0.05 was considered statistically significant in all analyses.

The study was performed in accordance with the National Ethic Committee and in agreement with the non-invasive examination of newborn children. This article has not been published elsewhere.

RESULTS

The results of the group of test group patients (n=20) and the control group (n=20) are presented in Figure **1**. There are significant differences between the two groups in the levels of IgE (3.441±0.785 versus 0.273±0.099 IU/mL, $p < 0.001$) and AGEs ($p < 0.01$). These results suggest that the newborns of allergic parents had significantly higher levels of AGEs. There was no difference in the blood glucose concentrations in mothers at the time of parturition. In neither newborns of allergic subjects ($r = - 0.1398$, $p = 54.2$) nor controls ($r = 0.1968$, $p = 51.4$) there were no correlations between IgE levels and AGEs.

DISCUSSION

The results of our study suggest that there is a significantly higher level of AGEs in newborns of allergic parents. This may be due to the fact that newborns already have an inborn predisposition to the development of allergy. The results indicate that predisposition to allergy may probably arise during intrauterine life. To the author´s best knowledge this is the first survey to demonstrate such findings. The strength of our study is that our children were clinically healthy term-babies. Another strength is that all blood samples were collected at the same point in time in the two groups.

Oxidative stress decreases immunity, the diminution of IL-1, IL-6 and influence expression of cytokines TNF-α [3]. The relationships are complicated and we cannot exclusively state, that oxidative stress causes immunodepression and conversely that antioxidant therapy results in immunostimulation. Activated phagocytes produce free radicals which are able to kill bacteria, viruses, yeasts and parasites. Furthermore, T-killer-cells kill tumor cells. Allergens and autoimmune diseases contain numerous free radicals. Free radicals oxidize or peroxidize proteins, lipoproteins, DNA etc. and thus change their properties. Intake of antioxidants during pregnancy may decrease the risk of allergies [4, 5] due to the decline of free radicals. Zinc and selenium through Fenton´s reactions may participate in autoimmune states. AGEs are formed both outside and inside the body. They are formed by the linkage of glucose usually to lysine residues. Other reactions may arise (Amadori, Schiff, Maillard products) where AGEs increase vascular permeability, inhibit vascular dilatation by blocking nitric oxide (NO), oxidize LDL-cholesterol, support cytokine production and increase oxidative stress [6].

AGEs are seen as speeding up oxidative damage to cells and in altering their normal behavior. Receptor for Advanced Glycation End products (RAGE) is found on many cells, including endothelial cells, smooth muscle, cells of the immune system from tissues such as lung, liver, and kidney. RAGE is expressed on T- lymphocytes, monocytes and macrophages. This receptor, when binding AGEs, contributes to allergy [7]. Determination of advanced oxidation products of proteins (AOPP) is a marker of oxidative stress. Significantly high levels of AOPP is associated with allergic rhinitis. AGEs cumulate during aging. The connection between AGEs and allergy is beyond the scope of this discussion. Patela and Lorenzo et al have described this most admirably [8, 9]. Mast cells produce AGE-binding protein, receptor to AGE (RAGE). Glycated albumin supports the extracellular release of superoxides from mitochondria, and thus damages calcium homeostasis (10). Apoptosis of mast cells contributes to the formation of inflammation [11]. Some AGEs have innate catalytic oxidative capacity. Stimulation of NAD(P)H oxidase through the activation of RAGE and damage to mitochondrial proteins leads to mitochondrial dysfunction and induces oxidative stress. As part of diabetic complications, AGEs agglomerate in proteins with a long half-life, and result in damage of retina, myelin, glomerular membrane and the vascular endothelium. AGEs generate reactive oxygen species (ROS) and activate inflammatory signaling cascades. In our previous work, we presented the results of a 12-year study, in which we examined 3600 samples of umbilical cord blood. We reached several conclusions from which it was clear that allergy was significantly associated with a positive family history [12].

The creation of glycated proteins is inhibited by phosphopyridoxal, guanidine, acetylosalicylic acid and D-lysin, though glycation of lysin is cancerogenic. Creation of AGE is faster than their degradation, which progresses after binding to RAGE. AGEs cause lipoperoxidation, cross-bonds, inactivate nitric oxide, stimulate the formation of cytokines, support free radical creation, cellular proliferation, and support coagulopathy. Studies in rats and mice have found that natural phenols such as resveratrol and curcumin can prevent the negative effects of the AGEs [13].

Early estimation of unbalanced oxidant-antioxidant and DNA damage may protectively influence the health of children [14, 15]. In contrast with healthy children, those with allergies have been found to have increased fractional exhaled nitric oxide (FeNO). Supplementation with vitamin E and selenium was observe to increase total antioxidant capacity - though only in asthmatics [16]. Further larger scale studies are needed to test the use of AGE and sRAGE as biomarkers for the prediction of allergy in children.

CONCLUSION

Our results suggest that newborns of allergic parents with higher levels of IgE have increased values of AGE in umbilical blood. We believe that the probability of future allergic reactions in children, whose mothers have allergy, may be higher when the level of AGE and IgE in umbilical cord blood is significantly increased. Because the levels of glucose between the two groups did not differ significantly we can conclude that the potentially allergic children have increased oxidative stress. This study has provided insights into new aspects of AGE in newborns and afforded important clues for further well-designed studies whether the increased level of free radicals can be diminished by administration of antioxidants.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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Declared none.

REFERENCES

[1] Bengmark, S.; Advanced glycation and lipoxidation and products-amlifiers of inflamation: the role of food. JPEN J. Parenter. Enteral. Nutr. 2007, 31 (5), 430-440.

[2] Henle, T.; Deppish, R.; Beck, W.; Hergessell, O.; Hänsch, G.M.; Ritz, E.: Advanced glycated end products (AGE) during haemodialysis treatment: discrepant results with different methodologies reflecting heterogeneity of AGE compounds. Nephrol. Dial. Transplant, 1999, 14(8), 1968-1975.

[3] Hrdý, J.; Žižka, J.: Expression of cytokines in cells of cord blood in the neonatal period of healthy and allergic mothers. Vox. Pediatriae, 2007, 10(8), 32.

[4] Nwaru, BI.; Erkkola, M.; Ahonen, S.; Kaila, M; Kronberg-Kippila, C.; Ilonen, J.; Simell, O.; Knip, M.; Veijola, R.; Virtanen, SM.: Intake of antioxidants during pregnancy and the risk of allergies and asthma of the offspring. Eur.J.Clin.Nutr. 2011, 65(8), 937-43.

[5] Matés, JM.; Peréz-Goméz, C.; Blanca, M.: Chemical and biological activity of free radical “scavengers“ in allergic diseases. Clin.Chim.Acta 2000, 296, 1-15.

[6] Vistoli, G.; DeMaddis, D.; Cipak, A.; Zarkovic, N.; Carini, M.; Aldini, G.: Advanced glycoxidation and lipoxidation and products (AGEs and ALEs) : an overwiew of their mechanisms of formation. Free Radic.Res. 2013, 47 (12), Suppl 1, 3-27.

[7] Aksoy, F.; Demirhan, H.; Veyseller, B.; Yildirim, YS.; Ozturan, O.; Basinoglu, T.: Advanced oxidation protein products as an oxidative stress marker in allergic rhinitis. Kulal Burun Bogaz Ihtis Derg. 2009, 19 (6), 279-284.

[8] Patella, V.; Incorvaia, C.; Minciullo, PL.: Oxidative stress markers in patients with hymenoptera venom allergy. Allergy Asthma Proc, 2015, 36, 9-13.

[9] Di Lorenzo, G.; Minciullo, PL.; Leto-Barone, MS.; La Piana, S.; La Porta, G.; Saija, A.; Gangemi, S.: Differences in the Behavior of Advanced Glycation End Products and Advanced Oxidation Protein Products in Patients With Allergic Rhinitis. J. Investig. Allergol. Clin. Immunol. 2013, 36, 101-106.

[10] Yoshimaru, T.; Suzuki, Y.; Inoue, T.; Nishida, S.; Ra, C.: Extracellular superoxide released from mitochondria mast cell death by advanced glycation end products. Biochim.Biophys.Acta 2008, 1783 (12), 2332-2443.

[11] Yan, SF.; Ramasamy, R.; Schmidt, AM.: Mechanisms of disease: advanced glycation end-products and their receptor in inflammation and diabetic complications. Nat. Clin. Pract. Endocrinol. Metab. 2008, 4(5), 285-293.

[12] Liška, J.; Siala, K.; Holeček, V.; Sobotová, Š.; Kepková, M.; Šefrna, F.: Effect of early treatment of newborns by peroral colonization by non-pathogenic *E. coli* on development of their immuno-allergic system. Bentham Science Publishers, Clinical Anti Inflammatory & Anti-Allergy Drugs, 2014, 1, 111-121.

[13] Mohammed, A. Hussein.; Hussein Abd El –Maksoud: Biochemical effects of Resveratrol and Curcumin combination on obese diabetic rats. Molecular & Clinical Pharmacology 2013, 4(1), 1-10.

[14] Chiavaroli, V.; Giannini, C.; De Marco, S.; Chiarelli, F.; Mohn, A: Unbalanced oxidant –antioxidant status and its effect in pediatric diseases. Redox Rep. 2011, 16(3), 101-107.

[15] 15. Zeyrek, D.; Cakmak, A.; Atas, A.; Kocyigit, A.; Erel, O.: DNA damage in children with asthma bronchiale and its association with oxidative measurements. Pediatr. Allergy Immunol. 2009, 20(4), 370-376.

[16] Motreno-Macias, H.; Romieu, I.: Effects of antioxidant supplements and nutrients on patients with asthma and allergies. J.Allergy Clin. Immunol. 2014, 133 (5): 1237-1234.