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The role of glucocorticoids in the treatment of acute anaphylactic reaction

Rola glikokortykosteroidów w leczeniu ostrej reakcji anafilaktycznej

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Abstract

Food allergy is a growing health problem, which is particularly common among the youngest children. Anaphylaxis, which is defined as a sudden-onset and potentially fatal response to an allergen, is an indication for urgent treatment. Although intramuscular epinephrine is the treatment of choice, all therapeutic algorithms also recommend glucocorticoids. They play an important role in reducing the risk of late allergic reaction, and, due to their non-genomic effects, are also increasingly often mentioned in the context of early response to shock. This effect is directly proportional to the dose of the drug, and a reduced duration of the symptoms of anaphylactic shock is achieved with the use of high doses of glucocorticoids. The paper presents a case of a 3-month-old girl with an anaphylactic reaction after consuming a modified milk preparation. After systemic administration of glucocorticoids, a satisfactory therapeutic effect was observed in the child.

Keywords: cow's milk protein allergy, anaphylaxis, food allergy, infants, glucocorticoids

Streszczenie

Alergia pokarmowa to coraz większy problem zdrowotny, który najczęściej dotyczy najmłodszych dzieci. Anafilaksja, czyli nagła i potencjalnie śmiertelna reakcja na alergen, stanowi wskazanie do natychmiastowego podjęcia leczenia. Lekiem z wyboru jest adrenalina podana domięśniowo, przy czym wszystkie algorytmy terapeutyczne zalecają również podanie glikokortykosteroidów. Mają one istotne znaczenie w zmniejszaniu ryzyka późnej reakcji alergicznej, są też – ze względu na działanie pozagenomowe – coraz częściej wymieniane w kontekście środków wczesnego reagowania na wstrząs. Działanie to zależy wprost proporcjonalnie od wielkości dawki leku, a skrócenie czasu występowania objawów wstrząsu anafilaktycznego uzyskuje się przy zastosowaniu dużych dawek glikokortykosteroidów. W pracy przedstawiono przypadek 3-miesięcznej dziewczynki z reakcją anafilaktyczną po spożyciu preparatu mleka modyfikowanego. Po podaży glikokortykosteroidów systemowo u dziecka zaobserwowano zadowalający efekt terapeutyczny.

Słowa kluczowe: alergia na białko mleka krowiego, anafilaksja, alergia pokarmowa, niemowlęta, glikokortykosteroidy

INTRODUCTION

Food allergy (FA) is a form of an adverse food reaction in which clinical symptoms are triggered and/or modulated by pathogenetic immune mechanisms[1]. It affects about 1–3% of adults and 4–6% of children. The incidence of FA depends on age and the allergens contained in different food products[2] (Tab. 1).

Hypersensitivity to cow's milk protein is the most common example of an allergy in developmental age[1]. Two groups of proteins are of clinical significance in this type of allergy: casein proteins and whey proteins [α-lactalbumin (Bos d 4), β-lactoglobulin (Bos d 5), bovine serum albumin (Bos d 6), bovine immunoglobulin]. Allergic reaction to α-lactalbumin occurs in approximately 80% of patients allergic to cow's milk protein. Clinical symptoms are very diverse and may occur in various clinical forms: gastrointestinal, cutaneous, respiratory or auditory. The clinical picture of food allergy may change during developmental age. Anatomical and functional maturation of organs and systems that are the site of allergic reactions promotes symptom regression in some patients. In other patients, the clinical picture may change, and they may develop new allergy symptoms.

Chandra et al. found that the pathogenetic mechanism of hypersensitivity was associated with an IgE-mediated reaction (type I according to the Gell and Coombs classification) in 48% of children allergic to cow's milk protein[4]. This reaction occurs within minutes to 4–6 hours after food consumption. **Anaphylactic shock** is the most severe, life-threatening form of IgE-mediated reaction. Several definitions of anaphylactic shock have been proposed in an attempt to provide the best possible clarification of the issue (Tab. 2)[5–11].

Food	Young children [%]	Adults [%]
Milk	2.5	0.3
Eggs	1.3	0.2
Peanuts	0.8	0.6
Nuts	0.2	0.5
Fish	0.1	0.4
Crustaceans	0.1	2.0
Total	6.0	3.7

Tab. 1. The prevalence of allergies to selected food products in children and adults[3]

The symptoms of anaphylaxis depend on the organ involved and the diagnosis is based on the clinical manifestations. In order to improve detectability, the European Academy of Allergy and Clinical Immunology (EAACI) Working Group on Anaphylaxis developed evidence-based guidelines for the diagnosis, risk assessment and treatment of patients who have previously developed or develop anaphylaxis (Tab. 3)[12].

A predisposed person may develop anaphylaxis in the absence of skin lesions or circulatory failure[13]. This form is most common in fatal cases. Cutaneous symptoms are absent in up to 10–20% of anaphylactic reactions, which may be the cause of late diagnosis[5].

Food is the most common cause of anaphylaxis (85% in the paediatric population). The youngest children usually develop anaphylaxis after consuming cow's milk protein and/or egg, whereas older children after consuming peanuts. Clinical signs occur within 30 minutes. Insect stings (mainly wasp and bee stings) are the second leading cause of anaphylaxis, with clinical symptoms developing within 15 minutes. The most rapidly developing anaphylactic shock (up to 5 minutes) occurs after ingestion of drugs, mainly β-lactam antibiotics and neuromuscular blocking agents[6].

Food-related anaphylaxis is the most common cause of death from an acute allergic reaction in children[14]. However, at the same time, a significant proportion of sudden hypertensive episodes may be mild, self-limiting and resolve without pharmacotherapy[15]. The unpredictable nature of an anaphylactic reaction justifies the need for immediate help and appropriate treatment.

Although various scales have been developed to assess the severity of anaphylaxis[16–18], none have been validated in

Society/organisation	Definition
WAO (2011)	A serious life-threatening generalised or systemic hypersensitivity reaction
EAACI (2013)	A severe life-threatening generalised or systemic hypersensitivity reaction
AAAAI/ACAAI (2010)	An acute life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden release of mediators from mast cells and basophils
ASCIA (2016)	Any acute onset illness with typical skin features (e.g. urticarial rash or erythema or flushing with or without angioedema), plus involvement of respiratory or cardiovascular symptoms with or without persistent severe gastrointestinal symptoms Any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present
NIAID (2006)	A serious allergic reaction that involves more than one organ system (for example, skin, respiratory tract, and/or gastrointestinal tract). It can begin very rapidly, and symptoms may be severe or life-threatening
WHO (2019)	A severe, life-threatening systemic hypersensitivity reaction characterised by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes

Tab. 2. Definitions of anaphylaxis by WAO (World Allergy Organization), EAACI (European Academy of Allergy and Clinical Immunology), AAAAI/ACAAI (American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology), ASCIA (Australasian Society of Clinical Immunology and Allergy), NIAID (National Institute of Allergy and Infectious Diseases) and WHO (World Health Organization). Elaborated by the authors

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Anaphylaxis is considered likely to be present if any of the following criteria are met:
Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus or flushing, swollen lips-tongue-uvula) and ≥1 of the following: • respiratory compromise [e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia] • reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia, syncope, incontinence)
≥2 of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): • involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula) • respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) • reduced blood pressure or associated symptoms (e.g. hypotonia, syncope, incontinence) • persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): • infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure • adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Tab. 3. Diagnostic criteria for anaphylaxis

population studies. Many factors that may predispose to a severe allergic reaction have been analysed. It is known that individuals allergic to peanuts and tree nuts are at the higher risk[19].

CASE REPORT

A 3-month-old female infant born from pregnancy 4, labour 3 by caesarean section due to lack of labour progress, with body weight of 3,410 g and an Apgar score of 10, was admitted to the paediatric emergency department due to weakness, wheezing, generalised urticaria with facial and cervical oedema and peripheral cyanosis. She had a medical and individual history of allergy.

Symptoms in the form of diffuse skin lesions (urticarial blisters) appeared on the erythematous skin about 20 minutes after the first administration of modified milk (the child was previously breastfed).

On admission, the infant was in a severe general condition, flaccid, with limited contact. Blood saturation was about 97–98%, heart rate was 119–160/min. Physical examination revealed wheals covering the entire body, peripheral cyanosis, oedema of the face and neck, and auscultatory symptoms – wheezing over the lung fields.

In the hospital emergency department, passive oxygen therapy was initiated using a simple oxygen mask (8 L/min). A venous access was established, through which a 10 mg bolus of prednisolone, and a drip infusion of 5% glucose with 0.9% NaCl (2:1) were administered. A standard dose (0.01 mg/kg body weight) of epinephrine was prepared, but its administration was postponed. The oedema of the face and neck began to regress, and the skin turned pink immediately after treatment initiation. After another few minutes, the severity of skin lesions decreased. A continuous infusion of prednisolone was started using a pump. Drip infusions through a second peripheral access were continued, and IV clemastine was included (at a dose of 0.5 mg). A glycerine suppository was administered to accelerate peristalsis and bowel movement.

Laboratory work-up on admission showed no blood count abnormalities (white blood cells, WBCs 11.5 thousand, lymphocytes 67%, neutrophils 19%). Inflammatory markers were low (C-reactive protein, CRP 0.1 mg/dL); kidney (creatinine 0.2 mg/dL, urea 11 mg/dL) and liver (alanine aminotransferase 30 U/L, aspartate aminotransferase 54 U/L) function parameters, as well as electrolytes (K^+ 5.9 mmol/L, Na^+ 140 mmol/L) were normal.

On day 3 of hospital stay, the infant developed fever (38.5°C) and auscultatory changes over the lung fields in the form of coarse crackles. Due to the baseline clinical condition, the diagnosis was extended to include chest radiography, which showed parenchymal densities. Ceftriaxone was included. Based on the overall clinical picture, the child was diagnosed with an anaphylactic reaction triggered by cow's milk protein and pneumonia. Possibly, the developing infection contributed to the severity of allergic response.

The child was discharged home on day 14 of hospital stay with recommendations to follow a dairy-free diet (amino acid-based formula) and to continue antihistamine treatment. The mother received a prescription for epinephrine in a prefilled syringe and was instructed on how to administer the medicine. Two months after the diagnosis of anaphylactic shock, the diagnosis for food allergy was extended to include immunoblot testing for specific IgE levels. Increased levels of IgE antibodies specific for cow's milk protein allergens (α-lactalbumin – class 2, β-lactoglobulin – class 2, casein – class 2) were found. Continuation of the elimination diet with the exclusion of products containing cow's milk protein was recommended.

DISCUSSION

According to published epidemiological data, food allergy accounts for 30–50% of all anaphylaxis cases[20]. Allergens in cow's milk, peanuts, eggs, tree nuts and grains are the most common causes of food-related anaphylaxis in children[21]. Sudden symptoms may occur at any age, as well as in children who previously tolerated a given food product. The spectrum of symptoms is very wide. In infants, the manifestation of anaphylaxis may be limited to sudden paleness and loss of muscle tone[22]. In the presented case, the symptoms of anaphylaxis occurred after intake of

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formula by a child with atopic dermatitis (AD). There is no evidence to link the severe course of anaphylaxis with AD[23]. However, there are factors known to contribute to and accelerate the development of anaphylactic reactions, i.e. cofactors. The most frequently mentioned cofactors are physical exercise, alcohol, non-steroidal anti-inflammatory drugs, menstruation and, as in the presented case, infection. Many symptoms of anaphylaxis are more difficult to interpret in children than in adults, and the child's medical history is based mainly on information provided by parents. Cutaneous symptoms predominate. A study published in 2012, including a cohort of 2,012 patients with anaphylaxis, showed that skin symptoms occurred in 84% of patients, followed by cardiovascular (72%) and respiratory symptoms (68%)[24]. The regression model showed a strong impact of age on respiratory and circulatory symptoms, with the former more common in children, and the latter dominant in adults. In the presented case, urticarial skin lesions dominated. Respiratory symptoms in the form of wheezing were also present.

Initiation of appropriate pharmacotherapy after diagnosis of an anaphylactic episode is critical for the patient's life. Epinephrine administered intramuscularly into the anterolateral aspect of the thigh is the gold standard[7]. There are no absolute contraindications for the use of epinephrine in a patient with anaphylactic shock, and the benefits of administering an appropriate dose outweigh the possible adverse effects. Antihistamines (H_1 receptor antagonists), oxygen therapy, infusion fluids, inhaled β_2-agonists, and nebulised epinephrine are the treatment of second choice[8]. In the presented case, no epinephrine was administered due to the resolution of skin and respiratory symptoms during the child's stay in hospital emergency department. Oxygen therapy, fluid therapy and systemic glucocorticoids (GCs) were used.

There is much controversy regarding the use of GCs in the acute phase of anaphylaxis, and the non-genomic mechanisms underlying their anti-inflammatory effects, which are increasingly well understood, undermine the current idea of the late onset of action of GCs[9]. The efficacy of these drugs in emergency conditions results from reducing the synthesis and/or release of various inflammatory mediators, which translates into inhibition of vascular changes such as dilatation and increased permeability, which are responsible for the main symptoms of shock, destabilisation of vital signs and multiorgan damage[10]. All therapeutic algorithms recommend GCs in medical emergency depending on anaphylactic reaction to inhibit the excessive pathological allergic response and reduce the risk of late symptoms. Molecular studies have shown that the contact of GCs with the cell membrane of an active immunocompetent blood cell (lymphocyte, mastocyte, basophil, eosinophil) activates various membrane mechanisms and intracellular systems that reduce the pathway and time to obtain the effect of pharmacotherapy, causing bronchial smooth muscle relaxation[11]. The effects of the extra-genomic mechanism depend on the GC dose – it should correspond to 5–10 mg of prednisolone per 1 kg of body weight (standard dose 1 mg/kg body weight)[25].

CONCLUSIONS

The pleiotropic action of GCs translates into a wide range of therapeutic effects, which cannot be achieved by other groups of drugs used in medicine. This strengthens the position of GCs in the treatment of emergencies related to anaphylactic shock.

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

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