Research article/Raziskovalni prispevek

THE INFLUENCE OF TREATMENT WITH ANTIBIOTICS IN THE FIRST YEAR OF LIFE ON THE PREVALENCE OF ASTHMA AND ATOPIC DERMATITIS IN CHILDREN

VPLIV ZDRAVLJENJA Z ANTIBIOTIKI V PRVEM LETU STAROSTI NA PREVALENCO ASTME IN ATOPIJSKEGA DERMATITISA PRI OTROCIH

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Abstract

Background — *Several factors have been implicated in the rising prevalence of allergic sensitisation and asthma. Early life exposure to allergens, viral and bacterial infections has an important influence on developing immune system. Human microflora and her changes in newborn and small child are very important for the maturation of the immune system. Frequent treatment with antibiotics alters the intestinal microflora and may lead to the development of allergic diseases.*
The purpose of this study was to assess the influence of treatment with antibiotics and choice of antibiotic in the first year of life on the prevalence of asthma and atopic dermatitis (AD) in 5 year old children.

Materials and methods — *582 children, exclusively breast-fed for 6 months, with a positive history of parental allergy, were included in this prospective study. At the age of one year they were divided into two groups according to whether they had been treated with antibiotics in the first year of life: group A: children treated with antibiotics; group B: untreated children. They were divided into three groups (groups I, II, III) according to the choice of antibiotic. Diagnosis of asthma and atopic dermatitis was ascertained with the ISAAC core, specific IgE testing and positive skin prick testes.*

Results — *29.5 % of children in group A developed asthma before the age of 5 years, compared to 4.7 % in group B. The prevalence of AD was higher in group A (39.6 %) than in group B (11.7 %). The differences between groups A and B were statistically significant ($P < 0.0001$). A higher prevalence of asthma and AD was found among children treated at least twice with antibiotics ($P < 0.0001$). Treatment with cephalosporins was associated with a higher prevalence of asthma ($P < 0.0001$).*

Conclusions — *The study confirmed that the use of antibiotics during the first year of life has an unfavourable influence on the prevalence of asthma and AD in 5-year-old children.*

Key words — *antibiotics; asthma; atopic dermatitis; child*

Izvleček

Izhodišča — *Za porast prevalence astme in alergijskih bolezni so odgovorni številni dejavniki. Izpostavljenost alergenom, virusnim in bakterijskim okužbam v prvih mesecih življenja vpliva na razvijajoči se imunski odziv. Ustrezna bakterijska kolonizacija prebavnega trakta novorojenca in malega otroka je pomembna za dozorevanje imunskega sistema. Pogosta zdravljenja z antibiotiki spremenijo črevesno mikrofloro in lahko povzročijo nastanek alergijskih bolezni.*
Namen raziskave je bil ugotoviti, kako vpliva izbira antibiotika in zdravljenje z njim v prvem letu življenja na prevalenco astme in atopijskega dermatitisa (AD) pri petletnih otrocih.

Preiskovanci in metode *V prospektivno raziskavo je bilo vključenih 582 otrok izključno dojenih 6 mesecev in s potrjeno alergijo pri starših. Glede na to, ali so bili zdravljeni z antibiotiki v prvem letu starosti, so bili razdeljeni v dve skupini: A – otroci, zdravljeni z antibiotiki, B – nezdravljeni otroci. Glede na izbiro antibiotika so bili razdeljeni v tri skupine (skupine I, II, III). Diagnozi alergijske astme in AD sta bili postavljeni v skladu s priporočili ISSAC raziskave, potrjeni s pozitivnimi kožnimi testi alergije z vbodno metodo in s povišano vrednostjo specifičnih IgE protiteles.*

Rezultati *Do petega leta se je pojavila astma pri 29,5 % otrok iz skupine A in pri 4,7 % otrok iz skupine B. AD je bil pogostejši v skupini A (39,6 %), kot v skupini B (11,7 %) (P < 0,0001). Prevalenca astme in AD je bila višja pri otrocih, ki so bili zdravljeni z antibiotikom dvakrat ali večkrat (P < 0,0001). Zdravljenje s cefalosporini je zvečalo pogostost astme (P < 0,0001).*

Zaključki *Raziskava potrjuje neugoden vpliv zdravljenja z antibiotiki v prvem letu starosti na prevalenco astme in AD pri petletnih otrocih.*

Ključne besede *antibiotik; astma; atopijski dermatitis; otrok*

Introduction

The prevalence of allergic diseases is increasing throughout the world, with the leap in the prevalence in recent decades being attributed to numerous factors. Apart from heredity, contact with allergens in the environment in early childhood is very important for the development of allergic diseases.[1, 2] The authors of the hygiene hypothesis postulate that limited exposure to infections during this period also contributes to their development.[3] The digestive system of the neonate is sterile. Bacterial colonisation plays an important role in the maturation of the immune response. Colonisation begins immediately after birth and is usually completed in the first week. The intestinal microflora changes until the third month of life, after which its composition stabilises. It is an important source of microbial stimulation for postnatal maturation of the immune system. Lactobacilli and Gram-positive cocci stimulate the formation of IL-12, which is critical for the shift from for the allergic inflammation typical Th2 to Th1 immune response. The Gram-negative bacteria E. coli stimulate the secretion of IL-10, which inhibit the Th1 immune response.[4] Alteration of the microflora and the child's age at which it occurs are crucial to the development of allergic diseases.[5,6] Their development is therefore indirectly stimulated by every intervention that affects the microflora. Studies in animals have confirmed that the function of the immune system is altered when the digestive tract is sterilised by antibiotics.[7] It has also been shown that treatment with antibiotics during this period alters the intestinal flora since antibiotics act non-selectively on both harmful and beneficial intestinal bacteria. The harmful effect is greater with frequent use of different antibiotics and if a broad-spectrum antibiotic is prescribed.[8]

The purpose of the study was to establish how treatment with antibiotics and the choice of antibiotic influence the development of asthma and atopic dermatitis (AD) in a group of Slovene children.

Subjects and methods

In the study, which was carried out in two parts, 582 children, born between December 1995 and January 2000 in the Northern Primorska region, were included. All parents gave written consent. All the children were born full-term with a birth weight of at least 3000 g and breast-fed at least 6 months. The crucial criterion for inclusion in the study was a positive family history of allergic diseases. From the family history it had to be evident that at least one parent, or a sibling, and possibly also one of the grandparents, had an allergic disease confirmed by allergy testing.

567 children, 291 boys and 276 girls, born before August 1999, participated in the first part of the study. At the preventive examination at the age of one year, they were divided into two groups according to whether they had been treated with antibiotics in the first year. Group A comprised 268 children who had been treated with antibiotics, while group B comprised 299 children who had not received antibiotics in the first year of life.

Only those children from the first part of the study who had been treated with antibiotics, and additional 14 out of 32 children, born between August 1999 and January 2000, who had a positive family history of allergic disease and were treated with antibiotics in the first year of life, participated in the second part of the study. This group consisted of 165 boys and 117 girls. At the age of one year data were obtained regarding the choice of antibiotic, how frequently it was prescribed and the reason for antibiotic treatment.

166 children were treated exclusively with penicillin – group I. 66 children were treated exclusively with cephalosporins – group II. 50 children were treated with three or more different antibiotics, but never with cephalosporins – group III. All were regularly followed-up and treated in the local children's health clinic, regardless of which group they belonged to. If signs of asthma developed at any time before the age of five years, the diagnosis was made on the basis of clinical history, examination, a positive response to

β2-agonist agents, and peak expiratory flow rate monitoring (PEF) in older children, and in accordance with recommendations of the ISAAC (International Study of Asthma and Allergies in Childhood) study. The latter recommends the use of standardised questions to establish the prevalence of allergic diseases, which would enable comparison between individual countries.[9]

The diagnosis of AD was made according to the diagnostic criteria for AD of Hanifin and Rajka, by which the diagnosis can only be made if the patient fulfils three major criteria (itching, skin involvement of sites characteristic of AD, chronic or recurrent dermatitis and a positive family history of atopic disease) and three minor criteria (dry skin, periauricular fissures, lower eyelid furrow, dermatitis of the palms and soles, deepened furrows of the palmar skin, ichthyosis, white dermographism, increased susceptibility to bacterial and viral skin infections, increased levels of serum antibodies and positive skin prick tests).[10] The allergologist in the regional hospital blinded to the child group allocation has confirmed the allergic origin of the disease with raised levels of specific serum IgE antibodies and positive skin prick tests during the diagnostic work-up or follow-up. At the preventative examination at the age of 3 and 5 years children with allergic asthma and AD were documented on the basis of examination of the child's medical records.

Differences between the groups were confirmed using the χ^2 test with Yates' correction. The value $P < 0.01$ was considered to be statistically significant. Data were analysed on a P. C. using the programme SPSS 11.0.

Results and discussion

600 children from 208 families took part in the study, which was conducted in two parts and ended in January 2005. The parents of 18 (3 %) of children refused to cooperate or did not respond to the invitation to the preventative examination. Boys (51.8 %) were in the majority.

Every treatment with antibiotics that lasted at least three days was counted, irrespective of who prescribed the medication (general practitioner, or on-call or hospital doctor) and for what illness it was prescribed. 48.5 % of children were treated with antibiotics in the first year of life. Given that a related study found that 70.7 % of children were treated with an antibiotic during this period, it can be concluded that antibiotic prescribing was rational in our patients.[11]

The majority of children (58.9 %) were treated with penicillin and only a minority (17.7 %) with cephalosporins. The latter were usually prescribed in hospital for the treatment of unexplained infections with a clinical picture of sepsis or severe infections of the lower respiratory tract and urinary tract. One fifth of children who were treated with cephalosporins received these medications for the treatment of a middle ear infection.

At the age of five years there were more children with asthma among those treated with antibiotics (29.5 %) compared to those who did not receive antibiotics in the first year of life (4.7 %) (Figure 1). Boys more often became ill in both groups. The difference in the prevalence of asthma between the groups confirms that treatment with antibiotics in early childhood is an important factor in its development in children who have a positive family history ($\chi^2 = 61.57$; $P < 0.0001$). The results of similar studies are contradictory. Some confirm the unfavourable influence of antibiotics on the development of asthma, while others show that there is no connection between treatment with antibiotics and the development of asthma during this period.[11, 12]

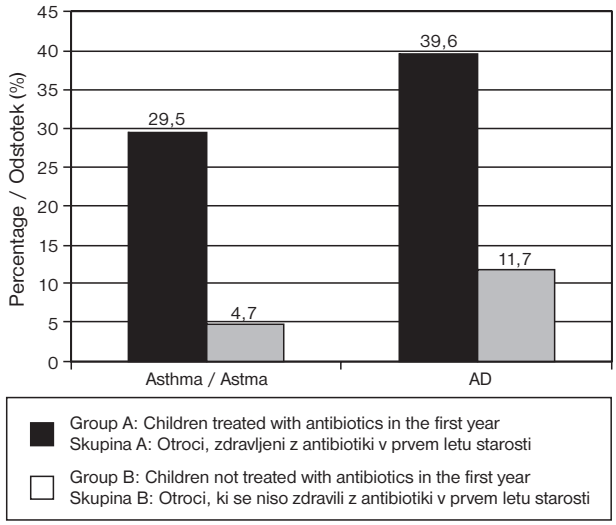

Figure 1. *The prevalence of asthma and AD according to treatment with antibiotics in the first year of life.*

Sl. 1. *Prikaz pogostosti astme in AD glede na zdravljenje z antibiotiki v prvem letu starosti.*

AD also occurred more frequently in children who were treated with antibiotics during this period (39.6 %), compared to those who were not (11.7 %), ($\chi^2 = 57.17$; $P < 0.0001$) (Figure 1).

Children who were treated with antibiotics at least twice had asthma and AD more frequently ($P < 0.0001$) (Figure 2). This finding additionally confirms the hypothesis that antibiotics influence the development of allergic disease and that their influence is also dependent on the number of times they have been prescribed. McKever et al. also confirmed a higher incidence of allergic diseases in children who were repeatedly treated with antibiotics.[13]

The hypothesis, that asthma and other atopic diseases develop because of an altered immune response, which is the result of treatment with antibiotics, was postulated on the basis of results of studies in mice.[14] Digestive tract microflora plays an important role in the maturation of the immune response. Quantitatively it is the most important source of microbial stimulation and gives the first signal for postnatal maturation of the immune response. Antibiotics change its composition and Th2 immune response is the conse-

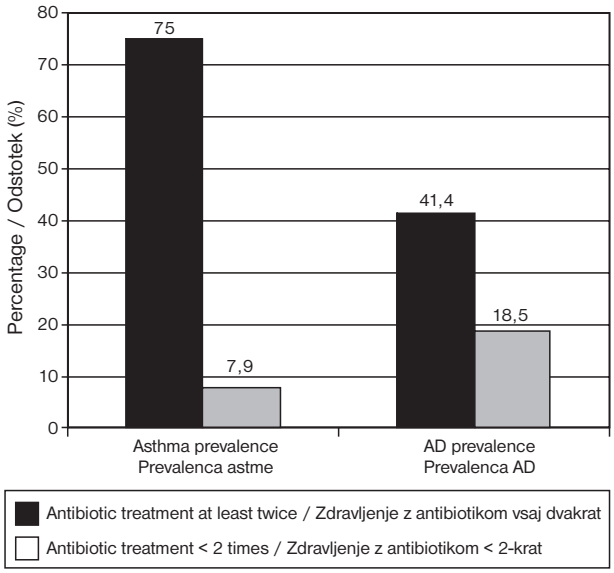

Figure 2. *The influence of the frequency of antibiotic treatment on the prevalence of asthma and AD.*

Sl. 2. *Vpliv pogostosti zdravljenja z antibiotikom na prevalenco astme in AD.*

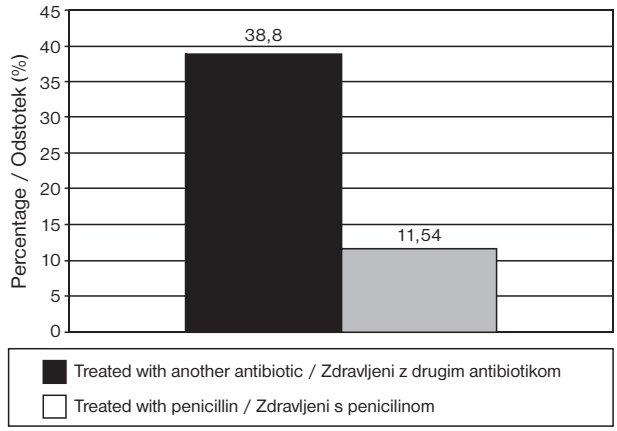

Figure 3. *Assessment of the influence of treatment with penicillin on the prevalence of asthma.*

Sl. 3. *Prikaz vpliva zdravljenja s penicilinom na prevalenco astme.*

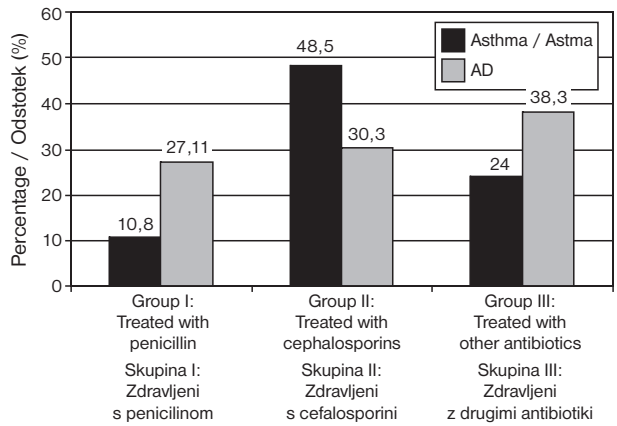

Figure 4. *Prevalence of asthma and AD regarding kind of antibiotic treatment.*

Sl. 4. *Prevalenca astme in AD glede na izbiro antibiotika.*

quence. The age of the child at which the alteration of the microflora arises is important.[4–6] The first three months of life, when the number and types of bacteria change considerably, are thought to be critical. When the microflora is established, it is very stable and less susceptible to various unfavourable influences. The deficiency of our study is that all treatment with antibiotics in the first year of life was included, regardless of when the treatment was prescribed: immediately after birth or in the twelfth month of life. Similarly, the duration of each course of treatment and the dosage were not taken into account. The influence on the intestinal microflora is also thought to be dependent on the dosage and frequency and duration of each course of treatment.

In their study Farooqi and Hopkin established that the type of antibiotic prescribed influences the development of asthma.[8] The probability that the illness will develop is lowest if penicillin is prescribed; this was also confirmed in the second part of our study. The frequency of asthma was higher whenever another antibiotic was prescribed instead of penicillin ($\chi^2 = 29.16$; $P < 0.0001$) (Figure 3). Cephalosporins in particular have been proven to increase the frequency of asthma ($\chi^2 = 29.16$; $P < 0.0001$), but they did not influence the frequency of AD ($\chi^2 = 4.02$; $P < 0.1338$) (Figure 4). The difference in the frequency of asthma between the groups could be influenced by parental, especially maternal, smoking habits. One hundred and six (18.2 %) children were exposed to tobacco smoke. Ninety-seven (16.6 %) of them were exposed to father's smoking. The percentage of children exposed to tobacco smoke was greater in group A (20.8 %) than in group B (17.4 %). The difference between the two groups was small and therefore we considered that the influence of exposure to tobacco smoke was not crucial to the greater prevalence of asthma.

In 81.2 % of episodes the antibiotic was prescribed for respiratory tract infection. In most cases the aetiology of the infection was unknown. The most frequent causative agents of infections are viruses. Antibiotics are not only ineffective against viral illnesses, but they also contribute to the development of allergic diseases and antibiotic resistance. 13.2 % of children took the antibiotic for a viral respiratory tract infection, since the parameters of inflammation were negative. It is known, that the majority of preschool children with asthma have a history of frequent lower respiratory tract infections with accompanying respiratory tract obstruction as early as the first year of life.[15] The latter could have been prescribed an antibiotic for signs of illness, which were the consequence of pre-existent, but still unrecognised asthma. Making the diagnosis of asthma in early childhood is, in fact, difficult. In the observed groups there were probably also some children who were treated with an antibiotic for exacerbations of asthma, especially in the second half of the first year of life. AD can also be treated by

antibiotics, but only exceptionally and only in the case of secondary bacterial infection. None of the children in the study group had been prescribed an antibiotic for AD. The predisposition to allergic disease was the same for all subjects as all had a positive family history of allergic disease, but those treated with antibiotics contracted allergic diseases more frequently.

Conclusions

The study confirms that treatment with antibiotics in the first year of life is an important factor for the development of asthma and AD in a group of 5-year-old Slovene children. The risk of their development increases if the child is repeatedly treated with antibiotics. Treatment with cephalosporins increases the prevalence of asthma. It is desirable that antibiotics are prescribed only when they are urgently required and, if possible, that penicillin is prescribed for children with a positive history of allergic disease.

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