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Mycoplasma pneumoniae as a trigger for Henoch-Schönlein purpura in children

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Abstract

Mycoplasma pneumoniae is one of the most common causes of respiratory tract infections in children. Extrapulmonary manifestations are seen in up to 25% of infected patients. Extrapulmonary complications are associated with the central nervous system, gastrointestinal tract, skin changes, myocarditis, pericarditis, hemolytic anemia, thrombocytopenia and thrombosis. The majority of extrapulmonary symptoms are associated with skin changes such as exanthematous skin eruptions, erythema nodosum, urticaria, Stevens-Jonson syndrome. M. pneumoniae stimulates production of the interleukins and tumor necrosis factor (TNF) α and can cause vasculitis. Henoch-Schönlein purpura (HSP) is a leucoclastic vasculitis that affects small vessels. Clinical manifestations of HSP include typical rash, arthritis, gastrointestinal and sometimes renal involvement. The main feature in HSP is abnormal IgA deposits in vessel walls. Circulating abnormal glycosylated IgA 1 and IgG antibodies form immune complexes: IgA1-IgG and anti-IgA 1. Immune complexes activate cytokines, parts of complement and influence directly the endothelium. We report cases of three children with Henoch-Schönlein purpura with prolonged and recurrent skin and joint changes. The serological analysis (positive serum IgM) confirmed Mycoplasma pneumoniae infection. Treatment with clarithromycin caused complete regression of disease. We suggest that in the case of prolonged symptoms of vasculitis due to Henoch-Schönlein purpura, Mycoplasma pneumonia infection may be a potential cause of exacerbation of the disease.

Key words: *children, Mycoplasma pneumoniae, Henoch-Schönlein purpura.*

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Introduction

Mycoplasma pneumoniae is a common bacterial pathogen causing respiratory tract infections in children. The incidence of morbidity increases with age and occurs in lower respiratory tract infections in 21.3% of children aged 2-4; 41.3% of children aged 5-7 years and nearly 60% of children over 7 years of age [1]. *Mycoplasma pneumoniae* belongs to a bacterial Mollicutes class and is characterized by the lack of cell wall, therefore cell-wall active antibiotics such as beta-lactams are ineffective against *Mycoplasma*. *Mycoplasma pneumoniae* lives only in humans, and the microorganism is spread by human-to-human contact with aerosol formation during coughing. Clinical symptoms of infection develop only in 3-10% of children after a contact with *M. pneumoniae.* The incubation period is about 14-21 days. The disease usually starts with non-specific symptoms such as pharyngitis, otitis, common cold, hoarseness, malaise and fever. The most common type of the infection with *M. pneumonia* is a lower respiratory tract infection [2, 3]. *Mycoplasma pneumoniae* can be associated with extrapulmonary manifestations even in 25% of patients. Extrapulmonary complications are associated with the central nervous system: meningitis, encephalitis, transverse myelitis, Guillain-Barré syndrome, but also with the gastrointestinal tract: nausea, vomiting, diarrhea, hepatitis and pancreatitis [4, 5]. Other complications can manifest as rashes, erythema nodosum, urticaria, arthritis, myocarditis, pericarditis, hemolytic anemia, thrombocytopenia and thrombosis [3, 6]. Similarity of bacterial antigens such as glycoproteins and glycolipids with human cells leads to immunological response with formation of immunological complexes and damage of the endothelium [7, 8]. *Mycoplasma pneumoniae* stimulates production of the interleukins and TNF-α and can cause vasculitis [9]. Henoch-Schönlein purpura (HSP) is the most common cause of vasculitis in children. The incidence of HSP in Caucasians is 4.6-14.6 /100 000 children. The highest number of patients is noted in autumn and winter [10]. The main pathophysiological feature in HSP is abnormal IgA deposits in vessel walls. It is related to reduced terminal glycosylation of the IgA1 in serum. Circulating abnor-

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mal glycosylated IgA1 and IgG antibodies form immune complexes: IgA1-IgG and anti-IgA1. Immune complexes activate cytokines, parts of complement and influence directly the endothelium. In the acute phase of HSP there can be detected increased concentrations of cytokines, such as TNF-α, which is a pro-inflammatory cytokine and it can cause damage to the endothelium.

Case reports

We present cases of three children with HSP. Diagnosis of HSP was based on the criteria of the Paediatric Rheumatology European Society (PRES), European League Against Rheumatism (EULAR) and Paediatric Rheumatology International Trials Organisation (PRINTO) [11,12]. In all patients with HSP, the infection of *Mycoplasma pneumoniae* was recognized by clinical symptoms and laboratory tests. On the 8th-10th day of the beginning of HSP we checked the titer of Mycoplasma-specific antibodies (ELISA, Genzyme Virotech GmbH, Germany). Serum IgG and IgM antibody titer values < 8.0 j/VE was negative, 9-11 j/VE borderline, > 11 j/VE was positive. We measured Mycoplasma-specific antibody titers after 14-20 days. Table 1 presents clinical data and the results of serological tests in patients with HSP and *M. pneumoniae* infection.

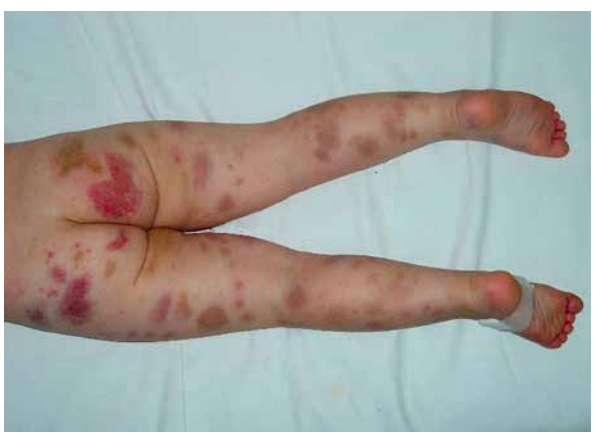

Fig. 1. Skin changes in patient No. 1

Case report 1

A 2.5-year-old girl, previously healthy, was admitted to the hospital because of the respiratory tract infection and erythema multiforme. On physical examination, petechiae and polymorphic rash with changes, 0.5 to 10 cm in diameter on buttocks, legs and feet were found (Fig. 1). Laboratory tests revealed increased inflammatory markers: CRP – 1.3 mg/dl (Normal value < 1.0 mg/dl), leukocytosis – 11.7 × 10^3/ul, ESR – 16 mm/1 h and IgA – 164 mg/dl (Normal value: 15-154). Urinalysis and serum creatinine (0.3 mg/dl) were normal. The girl received amoxicillin with clavulanic acid (90 mg/kg/day) for 7 days. After 5 days of treatment, inflammatory markers resolved, but because of recurrent skin changes, another etiology of the infection was suspected. Laboratory tests excluded tuberculosis, streptococcal infection, yersiniosis, toxoplasmosis, lambliasis, borreliosis, EBV and HSV infections. *Mycoplasma pneumoniae* infection was confirmed by a positive serological test (Table 1). Indication for the X-ray was the positive titer of antibodies against *M. pneumoniae*. X-ray of the chest revealed right-sided pneumonia without any changes on auscultation of the lungs. Treatment with clarithromycin at a dose of 15 mg/kg/day was started and was continued for 21 days. After 3 weeks of treatment, skin changes disappeared and the chest X-ray image was normal.

Case report 2

A 2.7-year-old girl was admitted to the hospital because of a suspicion of HSP. On physical examination, pharyngitis and polymorphic rash with petechiae on lower extremities, buttocks, and feet were found. On the right buttock, skin necrosis was seen (Fig. 2). Joints, particularly the knees and ankles, were swollen and painful. Laboratory tests revealed increased inflammatory markers: leukocytosis – 14.9 × 10^3/ul, ESR – 45 mm/1 h and IgA – 164

Table 1. Clinical symptoms and the titer of *Mycoplasma*-specific antibodies in patients with HSP and *Mycoplasma pneumoniae* infection.

Number of patients/sex	Age (years)	Clinical symptoms of Henoch-Schönlein purpura				Clinical symptoms of *M. pneumoniae* infection	Titer of *Mycoplasma*-specific antibodies (j/VE)	
		skin	joints	abdominal pain	kidney changes		IgM	IgG
1/F	2.5	+	+	–	–	pneumonia	18.4 22.4*	7.5 15.1*
2/F	2.7	+	+	–	–	upper respiratory tract infection, hepatomegaly	9.9 16.8*	36.2 28.3*
3/F	9	+	+	+	-	sinusitis	42.9	-

F – female
** control titer of Mycoplasma-specific antibodies measured after 14-20 days.*

mg/dl (normal value: 15-154); activity of liver enzymes: alanine aminotransferase – 32 U/l; (normal value: 20-60), aspartate aminotransferase – 24 U/l (normal value: l5-45), serum creatinine 0.3 mg/dl and urinalysis were normal. Hepatomegaly on ultrasonography was found. Laboratory tests excluded toxocarosis, yersiniosis, toxoplasmosis, lambliasis, borreliosis and chlamydia, RSV, HBV, HCV, CMV, EBV infections. The girl received amoxicillin with clavulanic acid at a dose of 90 mg/kg/day. Because of prolonged skin changes and a positive serological test of *M. pneumoniae* (positive IgM), amoxicillin with clavulanic acid (8 days) was switched to clarithromycin at a dose 15 mg/kg/day and continued for 14 days. After 2 weeks, all symptoms disappeared.

Case report 3

A 9-year-old girl was hospitalized with a suspicion of HSP. Two episodes of new skin changes have been observed for last 7 days. The patient was complaining about abdominal pain. On physical examination, the following findings were noted: polymorphic rash with petechiae, swollen joints, particularly the knees and ankles. Also carries, and systolic murmur 2/6 in Levine scale over the heart were found. Laboratory tests revealed normal inflammatory markers: CRP – 0.5 mg/dl, leukocytosis – 7.3 × 10^3/µl, ESR – 15 mm/1 h, normal concentration of IgA – 198 mg/dl (normal value: 57-233), normal liver enzymes, and serum creatinine (0.6 mg/dl) as well as urinalysis. Echocardiography was without abnormalities. Treatment with amoxicillin with clavulanic acid (90 mg/kg/day) was started. The girl needed a tooth extraction on the 7th day of treatment. Antibiotic treatment was complicated by pseudomembranous colitis with fever, vomiting, melena, and a positive occult stool test for blood. The girl received metronidazole for 10 days. Because the HSP was still active and we observed new skin changes, computed tomography (CT) of the head was performed to find another potential source of the infection. On CT, sphenoid and maxillary sinusitis were diagnosed, and because of these findings, serological tests for respiratory pathogens were performed. We confirmed *M. pneumoniae* infection and a successful treatment with clarithromycin (15 mg/kg/day) was started and was continued for 14 days. Skin changes resolved after 8 days of treatment.

All described patients had normal blood pressure, kidney function and number of platelets. Ultrasonography of the abdomen revealed the normal size and echogenicity of the kidneys. Coagulation system tests revealed that concentration of fibrinogen, APTT, and prothrombin time were normal. In patients 1 and 2, increased concentrations of D-dimers were observed – 4544 and 4837 ug/l FEU (N: 170-550), respectively, and which became normal within 7 days. Connective tissue diseases were excluded in all patients based on negative – anti-nuclear antibodies (ANA), and anti-neutrophil cytoplasmic antibodies (ANCA). Treatment of HSP included bed rest, etamsylate, ascorbic acid, rutoside and antibiotic therapy clarithromycin 15 mg/kg/day. This treatment led to remission of the disease and a favorable renal outcome at the 4-year follow-up.

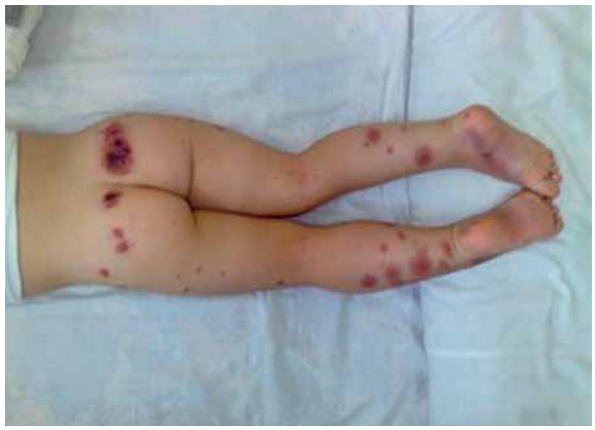

Fig. 2. Skin changes in patient No. 2

Discussion

Henoch-Schönlein purpura is a leucoclastic vasculitis that affects small vessels. Even though the diagnosis is obvious, the etiology remains unclear. The infectious agent triggers immunological reaction. The most difficult aspect in HSP is to find the specific trigger for leucoclastic vasculitis. Associations with bacterial and viral infection, immunization have been reported in the literature [13]. The most common cause of HSP is probably infection of the respiratory tract. In our patients, the trigger for HSP was an infectious agent *M. pneumoniae*. The association between HSP and *M. pneumoniae* infection is not very common. Terraneo *et al.* found 18 case reports of patients with HSP and *M. pneumoniae* infection confirmed by ELISA or PCR tests [14].

Clinical manifestations of HSP include typical rash, arthritis, gastrointestinal and renal involvement. Skin lesions of HSP are erythematous, urticarial papules that evolve to palpable purpura with hemorrhage, but the number of platelets is normal. The lesions are typically distributed symmetrically on legs, buttocks and sometimes on the upper extremities, especially elbow trunk and face. The total duration of the skin changes is usually 6-10 weeks, but up to 10% of patients develop chronic disease. Extracutaneous involvement includes arthritis, arthralgia, ankle edema, abdominal pain and renal complications. About 50% of patients with HSP present symptoms from the GI tract such as bleeding, emesis, severe abdominal pain, intussusceptions or paralytic ileus. The first symptoms usually appear on the eighth day of the disease. Less common manifestations of HSP are associated with testicular inflammation, changes in

the central nervous system or with pancreatitis [13, 15, 16]. The incidence of kidney involvement in HSP has been estimated as 30-50% of children [17]. The renal symptoms in HSP are quite variable. Patients with kidney complications demonstrate signs of nephritis: erythrocyturia, proteinuria, and hypertension or kidney injury. The clinical symptoms of HSP are well known and all our presented patients had typical changes for HSP on physical examination: skin and joint changes, abdominal pain. In all patients with infection and HSP, blood tests revealed increased inflammatory markers. Abnormal production of immunoglobulin IgA, which are deposited in vessels, causes vasculitis. Concentrations of IgA and IgA1 in serum are usually increased. Abnormalities in glycosylation of IgA1 lead to decreased metabolism of IgA1 in the liver. IgA-containing immune complexes are seen in vessels and skin and renal biopsies [13, 18]. In two described patients, concentrations of IgA were increased. Because of recurrent skin changes and prolonged activity of the disease we tried to find the etiological agent. In our patients prolonged activation of HSP was caused by *M. pneumoniae* infection confirmed by ELISA test. According to researchers, *M. pneumoniae* has majority of extrapulmonary symptoms like: skin changes such as exanthematous skin eruptions, erythema nodosum, urticaria, Stevens-Jonson syndrome and HSP [6, 7, 19-22]. Treatment of our patients with HSP included etamsylate, ascorbic acid, rutoside and antibiotic therapy. Treatment with macrolides led to remission of the disease.

Prognosis for children with HSP is good and the majority of children have spontaneous resolution of the nephritis. Only 2-12% can develop chronic kidney disease in the next 3-4 years [13]. In our patients, at the 4 years' follow-up we observed a favorable renal outcome.

Conclusions

Mycoplasma pneumoniae can be a trigger for Henoch-Schönlein purpura in children, and should be taken in consideration particularly in those with prolonged or recurrent episodes of HSP.

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