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Short communication
Kratko saopštenje

HIGH PREVALENCE OF AUTOANTIBODIES AGAINST MONOMERIC C REACTIVE PROTEIN (CRP) IN CHILDREN WITH PFAPA SYNDROME

VISOKA PREVALENCA AUTOANTITELA ZA MONOMERNI C REAKTIVNI PROTEIN (CRP) KOD DECE SA PFAPA SINDROMOM

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Summary

PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome is an autoinflammatory disorder of unknown etiology. The aim of our study was to evaluate whether the presence of anti-mCRP autoantibodies (anti-mCRP) might possibly contribute to systemic inflammation during PFAPA flares. We carried out anti-mCRP testing (in-house ELISA) in a single-center, prospective cohort of 30 PFAPA patients (12 girls). We found a high prevalence (43.3%) of anti-mCRP antibodies in PFAPA patients during their febrile episodes, which implies the possible involvement of anti-mCRP antibodies in PFAPA pathogenesis.

Keywords: anti-CRP, PFAPA, periodic fevers, autoimmune diseases

Kratak sadržaj

PFAPA (periodične groznice, aftozni stomatitis, faringitis, cervikalni adenitis) sindrom je autoinflamatorno oboljenje sa nepoznatom etiologijom. Cilj ove studije bio je da se utvrdi da li prisustvo anti-mCRP autoantitela (anti-mCRP) možda doprinosi sistemskoj inflamaciji tokom napada PFAPA. Sproveli smo anti-mCRP testiranje (interno sa ELISA) u jednocentričnoj prospektivnoj kohorti od 30 pacijenata sa PFAPA sindromom (12 devojčica). Otkrili smo visoku prevalencu (43,3%) anti-mCRP antitela kod obolelih od PFAPA tokom febrilnih epizoda, što ukazuje na potencijalno učešće anti-mCRP antitela u patogenezi PFAPA.

Ključne reči: anti-CRP, PFAPA, periodične groznice, autoimune bolesti

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Nonstandard abbreviations: anti-mCRP (autoantibodies against monomeric C reactive protein).

PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome is a periodic disease manifesting as recurrent episodes of systemic inflammation, characterized by high fever, cervical adenitis, pharyngitis and aphthous stomatitis (1). PFAPA is generally considered an autoinflammatory disease of compound etiology and heterogenous inheritance, but the exact pathogenesis and the underlying genetic variation remain unclear (2–5).

Monomeric CRP (mCRP) is an isomeric form of CRP with distinct antigenic and physiologic features. It has been suggested that anti-mCRP autoantibodies (anti-mCRP) interfere with mCRP's anti-inflammatory effect activity (clearance of immune complexes and apoptotic debris, complement-modulating effect) leading to an excessive inflammatory response (6-10). The presence of autoantibodies against mCRP has been detected in patients with systemic lupus erythematosus and other autoimmune diseases such as systemic scleroderma, rheumatoid arthritis, Sjögren's syndrome, autoimmune hepatitis, primary biliary cirrhosis, systemic vasculitis and TINU syndrome (8–16). We speculated that anti-mCRP might be present in patients with PFAPA syndrome and might be involved in the pathogenesis of PFAPA febrile flares. The aim of this study was to assess the prevalence of anti-mCRP in PFAPA patients during their febrile episodes.

Thirty children diagnosed with PFAPA syndrome in the Department of Paediatric Infectious Diseases of Wroclaw Medical University participated in the study. The diagnostic criteria were detailed in our previous report (17). The presence of anti-mCRP was tested with the use of in-house ELISA as described in the literature (18). Each sample was measured in quadruplicate, the specific absorbency value was normalized with 100% assigned to the reference high anti-mCRP lupus erythematosus serum value and the results were averaged. The cut-off value of the enzyme-linked immunosorbent assay was set as the mean ± 2 standard deviations of the 3 repeated measures for wells without serum and was 4% of the reference. Additionally, CRP and ESR were determined as part of a routine work-up. CRP levels were measured with immunoturbidimetric assay (Konelab, Thermo Fisher Scientific) and ESR was determined by standard methods.

The cohort consisted of 18 (60%) boys and 12 (40%) girls with a mean age of 4.3±2.1 years. The mean age at disease onset was 2.0±1.2. Mean duration of a febrile episode was 6 days with a 4.5-week interval between attacks. All patients presented with at least one of the main diagnostic features: pharyngitis (n=29), cervical adenitis (n=29) and oral aphtosis (n=20). All 3 symptoms were present in 19 patients, 10 children had 2 symptoms, and 1 patient presented with only one main symptom. Additional symptoms such as abdominal pain, arthralgias, skin rash, diarrhea, vomiting or headache were present in the majority (90%) of the patients. None of the patients had been receiving corticosteroid treatment before or at the time of blood sampling. The serum mCRP autoantibodies were detected in 13 patients (43.3%) with PFAPA syndrome during their febrile flares. As previously described (11), there was no association between anti-CRP levels and either CRP or ESR. No significant differences were found in age, gender, duration and frequency of the febrile attacks between those who were positive and negative for anti-mCRP.

We identified a high prevalence of anti-CRP antibodies in a single-center, prospective cohort of PFAPA patients. Our study has several limitations, such as the lack of control group and the single-center design. However, this is the first study to investigate the prevalence of anti-CRP in patients with periodic fever syndromes. Autoinflammatory conditions are disorders of innate immunity, characterized by absence of autoreactive antibodies and antigen-specific T-cells – the usual hallmarks of autoimmunity (3). However, PFAPA inflammatory response also involves Th1-type adaptive immunity (3–5), which dominates in several autoimmune diseases (19). Our results suggest that not only a cell-mediated immune response, but also an autoantibody production may play a role in the pathogenesis of PFAPA, linking the disease to autoimmune disorders. Thus, we further speculate that in terms of etiology, the disease should be placed somewhere in the spectrum between autoinflammatory and autoimmune conditions. Anti-CRP could be a target autoantigen in tonsillar and adenoidal tissues, which are inflamed during PFAPA flares. Considering the anti-inflammatory activity of mCRP (8–10), the presence of anti-mCRP might possibly contribute to a systemic inflammation during PFAPA episodes. Anti-mCRP obstructs the mCRP's complement-inhibitory effect, leading to an excessive complement activation. Involvement of the serum complement in PFAPA pathogenesis (mainly upregulated transcription of complement genes) has been implicated before (4).

In summary, we demonstrate that anti-mCRP are prevalent in patients with PFAPA syndrome. Further clinical and mechanistic studies are needed to verify our findings and evaluate the pathogenic role of anti-CRP in periodic fever syndromes.

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