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AUTOINFLAMMATORY DISEASES IN CHILDREN: NEW CHALLENGES

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აუტოანთებითი დაავადებები ბავშვებში: ახალი გამოწვევები

თსსუ-ის გ.ჟვანიას სახ. პედიატრიის საუნივერსიტეტო კლინიკა, საქართველო

რეზიუმე

აუტოანთებითი დაავადებები წარმოადგენს მნიშვნელოვან გამოწვევას პედიატრებისთვის, რაც განპირობებულია პოლიმორფული კლინიკური გამოვლინებებით და კომპლექსური პათოგენეზით. აუტოანთებითი დაავადებები ხასიათდება სხვადასხვა ხანგრძლივობის ცხელების შეტევებით, და ისეთი კლინიკური გამოვლინებებით, როგორიც არის მუცლის ტკივილი, ლიმფადენოპათია, პოლისეროზიტი, ართრიტი და ა.შ. კლინიკური გამოვლინების მრავალფეროვნების მიუხედავად, არსებობს რამდენიმე საერთო მახასიათებელი, კლინიკური სიმპტომატიკის მსგავსება, რაც აუტოანთებითი დაავადებების დიფერენციალურ დიაგნოზს ართულებს. ბავშვებში ისეთი აუტოანთებითი დაავადებების დიაგნოსტიკა, როგორიცაა PFAPA (პერიოდული ცხელება, აფთოზური სტომატიტი, ფარინგიტი და ადენიტი) და FMF (ოჯახური ხმელთაშუა ზღვის ცხელება), მნიშვნელოვან სირთულეებს წარმოადგენს სიმპტომების გადაფარვისა და გენეტიკური მუტაციების ვარიაბელურობის გამო.

Autoinflammatory disease represent the challenge to pediatricians for decades. In the autoinflammatory diseases, pathogenic inflammation arises through aberrant, antigen-independent activation of the immune system. Many of these diseases present with recurrent fevers and are termed the periodic fever syndromes, although other features may sometimes dominate the clinical picture.

The best characterized autoinflammatory diseases (AID) arise from mutations in single genes, but related mechanisms participate in many diseases in which inflammation contributes to tissue injury. Autoinflammatory diseases should be suspected when a patient presents with recurrent episodes of inflammation unexplained by another cause, such as infection or malignancy. Manifestations may include fever, rash, serositis (pleuritis or peritonitis), arthritis, meningitis, and uveitis. Lymphadenopathy and splenomegaly may also occur, and secondary (amyloid A) amyloidosis can complicate longstanding disease. Most patients develop their first disease manifestations in childhood.

The most challenging issue is that many autoinflammatory diseases (AID) share similar clinical features, as long as with some infectious diseases e. g Strep. Infectious and etc. Despite the advanced knowledge concerning autoinflammatory diseases (AID), more data regarding the optimal treatment options and outcomes of the children who met the criteria of more than one AID are required (Elif Kilic Konte et al).

PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) syndrome, which is characterized by recurrent episodes of fever associated with cervical adenitis, pharyngitis and aphthous stomatitis. The prognosis of this disease has been reported to be better than that of another autoinflammatory diseases. The etiology of the syndrome is not fully understood, although certain risk factors have been identified, as has a familial tendency to PFAPA. Most patients with PFAPA experience spontaneous resolution of symptoms without sequelae. However, the febrile episodes have shown to have a major impact on quality of life of children with PFAPA.

Familial Mediterranean fever (FMF) is a hereditary disorder characterized by acute attacks of fever, and serositis usually lasting for 1–3 days. FMF is caused by mutations in the Mediterranean Fever

gene (*MEFV),* which encodes the protein pyrin. Familial Mediterranean Fever (FMF) is characterized by recurrent attacks of fever and serositis (e.g., peritonitis, pleuritis, pericarditis, synovitis) or erysipelas-like erythema. Most patients with FMF experience their first attack in early childhood. Study done by Yonatan Butbul Aviel shows, that of 270 patients with PFAPA, more than one-half were of Mediterranean ancestry. Among patients with PFAPA, 51 (18.9%) also were diagnosed with FMF (PFAPA/FMF). The study shows a strong association between 2 common autoinflammatory syndromes, PFAPA and FMF, in patients from Mediterranean ancestry.

Does the presence of MEFV gene in clinical setting effect the treatment modalities? Colchicine has become a new treatment option in PFAPA. Study performed by Gulcin Otar Yener et al presents that: clinical phenotype and colchicine response of PFAPA patients were not affected by MEFV gene sequence variants.

When pediatrician should think about the autoinflammatory diseases, knowing, that early diagnosis is the very important for the management of these patients? Having delineated the most common monogenic hereditary periodic fevers, we should now attempt to establish in whom their presence should be suspected. Merav Lidar and Eitan Gidat proposed the most significant points for this issue:

- In the majority of cases, hereditary periodic fevers appear in early childhood and therefore pediatricians and family practitioners should be alert, especially when a positive family history or typical ethnic origin is present.
- In the same pediatric population, rapid appearance of fever without signs or symptoms of a respiratory or a urinary tract infection.
- Elevation of acute-phase reactants during attacks, with normalization of their levels during inter-critical intervals.
- Complete well-being between attacks.
- Repeated attacks and lack of seasonality: typically, 4–6 attacks over an observation period of 9–12 months are needed when basing a diagnosis only on clinical manifestations - this period may be shortened by confirmatory genetic testing.

Clinicians should be aware that presentation of one autoinflammatory disease may clinically evolve into another. Further studies are necessary to learn the correlation of various genetical mutations, clinical manifestations and treatment options.

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SUMMARY

Autoinflammatory diseases are a significant challenge for pediatricians due to polymorphic clinical manifestations and complex pathogenesis. Autoinflammatory diseases are characterized by fever attacks of varying duration, and clinical manifestations such as abdominal pain, lymphadenopathy, polyserositis, arthritis, etc. Despite the variety of clinical manifestations, there are several common characteristics, similarities to clinical symptoms, which complicate the differential diagnosis of autoinflammatory diseases. Diagnosing autoinflammatory diseases such as PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) and FMF (Familial Mediterranean Fever) in children presents significant difficulties due to overlapping symptoms and variability of genetic mutations.

Keywords: autoinflammatory, diseases, children, new challenges, PFAFA, FMF