Coexistence of Familial Mediterranean Fever and Hyperimmunoglobulinemia D Syndrome in a Child

Bir Çocukta Ailesel Akdeniz Ateşi ve Hiperimmünglobulin D Sendromu Birlikteliği

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Özet

Kalıtsal otoinflamatuvar sendromlar olarak bilinen kalıtsal periyodik ateş sendromları Mendeliyen kalıtımlı tek gen hastalıklardır, tekrarlayan ateş ve enflamasyon atakları ile karakterizedir. Ailesel Akdeniz Ateşi ve Hiperimmünglobulin D sendromu bunların prototipleridir ve otozomal resesif olarak kalıtılır. Tanı klinik seyir,aile öyküsünü temel alır ve genetic mutasyon analizi ile doğtulanır. İki yaşından beri tekrarlayan ateş, cilt döküntüsü ve servikal lenfadenopati atakları olan beş yaşında erkek çocuk sunulmuştur. Genetik analizinde MEFV ve MVK genlerinde sırasıyla homozigot M694V ve V377I mutasyonları saptanmıştır. Yaptığımız literatür araştırmasına göre hastamız hem Ailesel Akdeniz Ateşi hem de Hiperimmünglobulin D sendromu klinik ve genetik özellikerini taşıyan ilk olgudur.

Anahtar Kelimeler

Ailesel Akdeniz Ateşi; Hiperimmünglobulin D Sendromu; Çocuklar

Abstract

Hereditary periodic fever syndromes are Mendelian inherited single gene diseases which are also known as hereditary autoinflammatory syndromes, are characterized by recurrent attacks of fever and inflammation. Familial Mediterranean Fever and Hyperimmunoglobulinemia D syndrome are prototypes and are inherited autosomal recessively. The diagnosis is based on clinical course, family history and is confirmed with genetic mutation analysis. We describe a 5- year-old boy who had recurrent attacks of fever, skin rash, and cervical lymphadenopathy since he was 2 years old. His genetic analysis revealed homozygous M694V and V377I for MEFV and MVK gene respectively. Due to our knowledge, this is the first report of a patient who has both HIDS and FMF clinical and genetic features.

Keywords

Familial Mediterranean Fever; Hyperimmunoglobulinemia D Syndrome; Children

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Introduction

Hyperimmunoglobulinemia D syndrome (HIDS) is one of the members of hereditary periodic fevers which is autosomal recessively inherited and is characterized by recurrent fever attacks of abdominal pain, arthralgia/arthritis, skin lesions, headache, lymphadenopathy (LAP), diarrhea and apthous ulcer. The diagnosis is based on characteristic clinical findings and elevated levels of IgD (>100 U/ml) and it is confirmed by demonstrating deficient MVK enzyme activity or by identification of disease causing mutation on MVK gene [1].

Familial Mediterranean Fever (FMF) is autosomal recessively inherited prototype of hereditary periodic fevers. The characterized clinical findings are recurrent episodes of fever, serosal inflammation and rash described as erysipelas like erythema. The diagnosis of FMF is based on characteristic clinical course, family history and physician's experience [2].

In periodic fever syndromes patients' inflammatory response is set wrongly and is not terminated at the appropriate time [3]. Isoprenoid pathway and also pyrin's effect on caspase-1 mediated activation of IL-1B is responsible for inflammation in the pathogenesis of HIDS and FMF respectively [4].

Although FMF and HIDS are rare autosomal recessive disorders, coexistence in a patient was not reported previously. We present a 5-year-old boy with HIDS and FMF due to rare association.

Case Report

A 5-year-old Turkish boy was admitted to our pediatric clinic with abdominal pain, fever and rash. These complaints have been occurred every 2 or 3 weeks, lasted 3 days since 2 years old. During fever attacks, he had abdominal pain, malaise, arthralgia and cervical lymphadenopathy. He also developed maculopapular rash on his extremities. His parents were not consanguineous and family history for periodic fever was negative. On admission physical examination showed growth retardation (body weight and height <3p), purpuric lesions on lower extremities, pallor and cervical microlymphadenopathy.

Laboratory studies revealed leukocyte count 4900/mm3, hematocrite 33.3%, platelet count 385000/mm3, fibrinogen 367 U/L, serum amyloid A 8 mg/dL, C reactive protein 28.8 (0-5 mg/L) and erythrocyte sedimentation rate 42 mm/hour. Urinalysis was normal and test for occult fecal blood was positive. Antinuclear antibody and antineutrophil cytoplasmic antibody were negative. Investigations for vasculitis, porfiria and auto immune lymphoprolifreative syndrome were negative. The serology for various viral and bacterial infectious agents was negative. Enlarged mesenteric lymph nodes were shown in abdominal ultrasonography. Serum immunoglobulin levels were as given: IgA 2.06 gr/L, IgG 14.1 gr/L, IgE 1280 IU/mL, IgD level 160 U/L (the repeated value one month later was 148 U/L). Mutation analysis of MEFV gen for FMF and MVK gene for HIDS revealed that he was homozygous for M694V and V377I respectively.

According to these clinical and laboratory findings diagnosis of HIDS and FMF was proposed and colchicine was started. He did not have any attack for two years.

Discussion

Periodic fever in children is regarded as a rare entity, but is not uncommon [2]. Characteristic features of periodic fevers, a subgroup of autoinflammatory diseases, are recurrent attacks of generalized inflammation. Autoimmune or infectious causes can not be identified. HIDS and FMF are both autosomal recessively inherited disorders and they have different clinical, epidemiologic and genetic characters. Molecular genetic defects on different chromosomes have helped us to differentiate periodic fever syndromes and will provide new insight to the pathogenesis [1, 3]. MEFV gene is cloned on chromosome 16, which is responsible for FMF, is different from the gene MVK mapped on chromosome 12, which is responsible for HIDS [1, 2].

Recent studies have demonstrated links between the isoprenoid pathway and inflammation [3]. Mutation of MVK gene causes a reduction of MK enzyme activity in HIDS which is a component of this pathway [1]. In the pathogenesis of HIDS the role of IL-1B is demonstrated by increased ex vivo production of the cytokine and successful treatment with IL-1 blocker anakinra [5]. MEFV gene encodes a protein pyrin (or marenostrin) whose expression is stimulated by inflammatory mediators and has an inhibitory effect on caspase-1 mediated activation of IL-1B. IL-1B is a key mediator of inflammation [6]. It is interesting that, in spite of activation of two different pathways for IL-1B synthesis the clinical phenotype of our patient was not so severe.

HIDS generally occurs during the infant period. The common symptoms of HIDS are arthralgia, arthritis, malaise, erythematous macules, petechia and purpura during fewer attacks [1]. Diarrhea, abdominal pain, cervical LAP generally accompanies the attacks. Infections, stress, minor trauma or surgery can provoke the attacks. Oral and genital apthous ulcers also have been reported [4]. Our patient showed all these signs and symptoms. The attacks were provoked by upper respiratory tract infections. Diarrhea was also seen during the last 2-3 days of attacks.

The clinical picture including recurrent peritonitis and arthralgia with fever pointed out FMF and genetic analysis revealed homozygous for M694V [7].

Although skin lesions are common in patients with HIDS [8], a recent study showed that elevated IgD levels in FMF patients were associated with erysipelas like erythema [2]. In our patient, severe skin lesions and the early onset of the symptoms aroused the suspicion of HIDS. Therefore, we first examined IgD levels. Elevated IgD level was reported in patients with other periodic fever syndromes, including FMF and TRAPS [9], but in that study MVK gene mutation were not studied. In our case, we measured serum IgD levels at two occasions with at least one month apart and than examined V377I mutation analysis for MVK gene. Due to our knowledge, FMF and HIDS coexistence has not been reported before.

HIDS registry in Nijmegen, Netherlands, currently has data on over 200 cases 126 of them were confirmed with mutation analysis and one of them from Turkey [10]. Our patient is the second Turkish case reported from Turkey, whose diagnosis was confirmed with homozygous V377I mutation analysis.

In conclusion, this case clearly showed that although HIDS and FMF are clinically, immunologically, and genetically different entities they could be superposed in the same patient. Severe skin lesions seemed to be associated with this clinic entity.

Competing interests

The authors declare that they have no competing interests.

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