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# Mevalonate kinase deficiency/Hyperimmunoglobulin D syndrome (MVK/HIDS) in a Differential Diagnosis of Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis (PFAPA) Syndrome and Familial Mediterranean Fever (FMF): A Case Report

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Autoinflammatory diseases represent a heterogeneous group with recurrent attacks of inflammation.[1] The clinical presentation includes periodic attacks of fever, rash, and organ-specific inflammatory pattern including peritonitis, pleuritis, arthritis, meningitis, and orchitis.[2] Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease in our region, characterized by self-limiting attacks of fever and serositis.[3] On the other hand, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is periodic fever syndrome of unknown origin.[4] Although familial clustering has been reported, no clear cause has been identified yet.[5,6] Another monogenic autoinflammatory disorder characterized by recurrent fever accompanied by abdominal pain, vomiting, diarrhea, and cervical lymphadenopathy is mevalonate kinase deficiency/hyperimmunoglobulin D syndrome (MKD/HIDS).[6,7] The underlying causes of this very rare autosomal recessive disease are pathogenic variations in the *MVK* (Mevalonate Kinase) gene.[8] The differential clinical manifestations of this disease are indicated in Table 1.

In this paper, we aimed to present a 15-year-old female patient who was referred to our clinic with complaints of recurrent fever and abdominal pain that started at the age of 4. The patient was admitted to our clinic for the first time with complaints of severe abdominal pain and fever lasting for 2 days. Her parents stated that the same symptoms recurred every 2-3 weeks, periodically, for the last 3 months. During the disease attack, body temperature is measured as 38.5 ˚C with abdominal tenderness and rebound. No splenomegaly, hepatomegaly, arthritis, or rash were observed on physical examination. Laboratory test revealed anemia and increased acute phase markers, at the initial evaluation at the disease attack: HGB 10.6 g/dL, HCT 31.9, MCV 72.5 fl, MCH 24.1 pg, AST 30 IU/L, ALT 13 IU/L, PLT 355 $10^3$/μL, WBC 9200/$mm^3$, ESR 45 mm/h, and CRP 6.8 mg/dL. The microbiological evaluation remained negative including nasopharyngeal swab culture, hemoculture, and urinoculture. The patient was initially diagnosed with FMF due to the clinical findings compatible with FMF, consanguineous marriage history, and Turkey being an endemic country for the disease.[9,10,11] Accordingly, colchicine treatment (2 × 0.5 mg/day p.o.) was started after excluding possible other causes (e.g., malignancy, infection, other inflammatory disorders). In the following 3-month control appointments, no significant finding was detected in the physical examination. The frequency of attacks decreased but sporadic recurrent fever, abdominal pain, and diarrhea continued. The patient's treatment was continued by increasing the colchicine dose to maximum tolerable (2 × 1 mg/day p.o.). In the further follow-up, the frequency of attacks slightly decreased (2 attacks in 3 months). The detailed re-evaluation of the patient revealed the recurrent attacks of fever accompanied by lymphadenopathy and cryptic tonsillitis that were often treated by oral antibiotics by the related pediatrician. All symptoms were compatible with the diagnosis of PFAPA syndrome, so a single dose of prednisolone was administered at the disease attack. The dose of prednisolone is 1 mg/kg dose.[4,6,12] The patient responded promptly with regression of all symptoms

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**Table 1.** Common Features and Main Differences Among Patients with Familial Mediterranean fever, PFAPA syndrome, and Mevalonate kinase deficiency/Hyperimmunoglobulin D syndrome.

| Clinical findings | FMF | PFAPA syndrome | MVK/HIDS |
|---|---|---|---|
| Abdominal pain | ++ | +/– | ++ |
| Aphthous stomatitis | – | ++ | + |
| Arthritis | – | + | +/– |
| Cervical lymphadenopathy | – | + | + |
| Erysipelas like erythema | + | – | – |
| Positive Family history | + | +/– | – |
| Fever | + | + | + |
| Pharyngitis | – | ++ | +/- |
| Pleurisy | + | – | – |
| Regularity of the episodes | – | ++ | – |
| Response to the single dose of glucocorticoids | +/– | + | +/– |
| Response to colchicine | + | +/– | +/– |
| Response to anti-IL-1 agent | + | +/– | ++ |
| Gene mutation | *MEFV* | – | *MVK* |
| Increase in acute phase reactants | + | + | + |
| Diarrhea | - | - | ++ |
| Rash | - | - | ++ |
| Normal growth and development | + | + | +/- |
| Cryptic tonsillitis | – | ++ | +/– |

FMF, familial Mediterranean fever; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; HIDS, hyperimmunoglobulin D syndrome; gc, glucocorticoids; MVK, Mevalonate Kinase; MEFV Familial Mediterranean fever gene

and physical findings. The patient was confirmed with PFAPA syndrome in addition to FMF, so the colchicine treatment continued and the single dose of corticosteroids was suggested at the time of the PFAPA attack. In the follow-up, the frequency of attacks increased despite the good response to corticosteroid treatment applied at attacks. Since PFAPA syndrome attacks accompanying FMF caused significant damage to the patient's quality of life, it was decided to perform tonsillectomy and colchicine treatment was maintained. Although the frequency of attacks decreased, the complete remission was not achieved with the persistent elevation of acute phase markers in laboratory examination (namely, erythrocyte sedimentation rate, C-reactive protein).

At the age of 12, the patient has been admitted to the pediatric emergency department due to fever, abdominal pain, and diarrhea. Physical examination revealed cervical lymphadenopathy and maculopapular rash in the chest that were not compatible with the diagnosis of FMF.

When re-evaluated the patient's disease history and current complaints (inadequate response to colchicine, PFAPA attacks despite the tonsillectomy, maculopapular rash of the chest), the autoinflammatory condition other than PFAPA syndrome and FMF was considered. Further genetic evaluation including whole-exome sequencing revealed homozygous p.Val377Ile (c.1129G>A) (reported allele frequency: 0.001578)[13] and heterozygous p.Ile268Thr (c.803T>C) (reported allele frequency: 0.0001556)[13] pathogenic variations in the *MVK* gene, in addition to heterozygous p. Met694Val (c.2080A>G) (reported allele frequency: 0.0002722)[13] pathogenic variation in the *MEFV* gene.

Accordingly, anakinra (interleukin (IL)-1 receptor antagonist) was added to the treatment. The patient responded well to anti-IL1 treatment with cessation of disease attacks and regression in acute phase markers. However, anakinra injection caused an allergic reaction in the applied area so it was replaced by canakinumab (IL-1 beta inhibitor). During the last 6 months, the patient is asymptomatic and control laboratory tests were in normal ranges: HGB 11.7 g/dL, HCT 35.5, MCV 76.5 fl, MCH 25.2 pg, AST 18 IU/L, ALT 12 IU/L, PLT 290 $10^3$/μL, WBC 7500/$mm^3$, ESR 6 mm/h, CRP 2.5 mg/dL. The patient's treatment continues with colchicine (3 × 0.5 mg/day p.o.) and canakinumab (150 mg s.c. per month).

Both variations in the *MVK* gene and the one in *MEFV* are pathogenic, so it will be relevant to know the parental carrier pattern. Unfortunately, the genetic testing of the parents has not been performed, which we consider as a limitation of our paper.

Although PFAPA syndrome represents the most common autoinflammatory condition worldwide, the other possibilities should be taken into consideration. The recurrent fever attacks accompanied by prominent lymphadenopathy, abdominal pain, gastroenteritis, and maculopapular rash are suggestive of conditions other than FMF and PFAPA syndrome.

As Gattorno et al. discussed in their paper, PFAPA syndrome criteria are not able to distinguish genetically positive patients from genetically negative patients. Thus, the proposed Gaslini score was shown to be able to perform very well in distinguishing genetically negative from genetically positive patients with PFAPA syndrome.[14]

By this case, we emphasized the significance of genetic testing, especially in patients with symptoms suggestible for autoinflammatory conditions. Although the clinical features could lead to diagnosis, in certain cases, especially those with features atypical for commonly seen conditions, clinicians should be encouraged for apply to genetical testing.

In conclusion, periodic fever accompanied with abdominal pain and increased acute phase markers is highly suggestive for diagnosis of FMF, especially in endemic regions. It should be kept in mind that many autoinflammatory diseases may show similar symptoms and may respond partially to colchicine. For this reason, it is critical to evaluate the patients' history in detail and perform the physical examination during the disease attack.

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