CASE REPORT

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Mevalonic Aciduria Presenting with Recurrent Perianal Fistulas

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ABSTRACT Mevalonic aciduria (MA) is a severe and rare clinical entity characterized by growth failure, neuropsychomotor development delay, dysmorphic features, periodic fever episodes of involving joints, abdominal organs and skin. Severe gastrointestinal involvement, perianal or gastrointestinal ulcers can be seen rarely.MA is caused by mutations in the gene encoding mevalonate kinase, with the degree of residual enzyme activity largely determining disease severity. Mevalonate kinase is crucial for the biosynthesis of nonsterol isoprenoids, which mediate protein prenylation. These gene defects not only intervene in the mevalonate pathway of cholesterol synthesis but also give rise to episodes of hyperinflammation with increased secretion of interleukin 1b (IL-1β). Although the precise pathogenesis of MA remains unclear, increasing evidence suggests that deficiency in protein prenylation leads to innate immune activation and systemic hyperinflammation. Recent treatment approaches have focused mainly on cytokine-directed biologic therapy because of the understanding of MA as an autoinflammatory disorder. In this paper, we present a 22-year-old female patient with MA disease who had been suffering from recurrent fever attacks, perianal abscesses, and fistulas since her infancy. She has been followed in our clinic since the age of 15 years. She was successfully treated with canakinumab. IL-1 blockade appears to be effective in treating the gastrointestinal complications of MA.

Keywords: Mevalonic acidiuria; perianal abcess; perianal fistulas; interleukin-1 blockade

Mevalonate kinase deficiency (MKD), a very rare autosomal recessive autoinflammatory disease with various organ involvement manifests clinically as hyperimmunoglobulinemia D syndrome, a more common and less severe phenotype form, and mevalonic aciduria (MA), a rare form and more severe phenotype. The onset of the disease is within the first year of life. The febrile attacks of MKD usually occur every 2-8 weeks and last 3-7 days. Patients with MA typically present developmental delay, physical dysmorphisms, psychomotor retardation, ocular abnormalities and hepatosplenomegaly besides autoinflammatory attack.[1] The symptoms of MA begin in the first months of life, with antenatal manifestations related with a high rate of stillborns in affected families. Gastrointestinal findings comprise few cases of cholestasis and liver dysfunction.[2] However, perianal and rectovaginal fistulas are extremely rare. Here, we present a very rare form of MA that accompanies perirectal abscess and rectovaginal fistulas, which was successfully treated with canakinumab.

CASE REPORT

A 15-year-old female was referred to our hospital with a history of recurrent fever attacks, arthritis, lymphadenomegaly, sinopulmonary infections, and perianal fistulas. She had recurrent peripheral facial nerve paralysis, gait disturbance, mental retardation and dysmorphic face. The patient was the third sibling of a non-consanguineous family. The symptoms of the patient alongside her age of development were shown in Figure 1. The onset age of inflammatory attacks was six months, and perianal and rectovaginal fistulas and abscess developed when the patient turned four years old. She was operated on four times because of the rectovaginal fistulas. Due to recurrent diarrhea and abdominal pain attacks, colonoscopy

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was performed, and the histopathologic examination revealed nonspecific inflammatory changes. Laboratory blood tests taken during the inflammatory attacks affirmed raised serum amyloid A (SAA) 578 mg/L, (N: <10), high C-reactive protein 200 mg/L (N: 0-5), and erythrocyte sedimentation rate 120 mm/h (N: <15). Anti-nuclear antibodies, rheumatoid factor, lymphocyte subgroups, and immunoglobulin (Ig) G: 1,630 mg/L (N: 913-1,884) and IgM: 250 mg/L (N: 88-322) were normal. Anti-ds DNA, perinuclear anti neutrophil cytoplasmic antibody, cytoplasmic anti-neutrophil cytoplasmic antibody were found negative as well. The level of serum IgA was persistently high (954-864 mg/L, reference range: 139-378 mg/L). The antibody titers against diphtheria and tetanus vaccines were normal. She was commenced on colchicine due to recurrent inflammatory attacks.

Increased mevalonic acid excretion was detected in the urine during the attacks. The genetic analysis done by using Fever & Auto-inflammatory Diseases Kit by Sophia-Genetics found compound heterozygosity for the common c.1129G>A (p.V377I) mutation and p. Gly 18Arg (c.52G>A) mutation. Cranial magnetic resonance imaging (MRI) revealed cerebellar and corpus callosum atrophy associated with vermian hypoplasia.

The patient had left follow-up for 6 years, on admission after treatment for 2 years with nonsteroidal anti-inflammatory drug (NSAID), colchicine was started firstly, she has been receiving for 7 years. She had limping for the last six months and a sacroiliac MRI showed unilateral sacroiliitis (left). With the diagnosis of MA associated with high SAA level, canakinumab treatment was started at the age of 22. She was also commenced on angiotensin-converting enzyme inhibitor treatment due to proteinuria and renal amyloidosis. Fever attacks and rectovaginal fistulas receded and acute phase proteins decreased 2 months after starting monthly canakinumab treatment (Table 1).

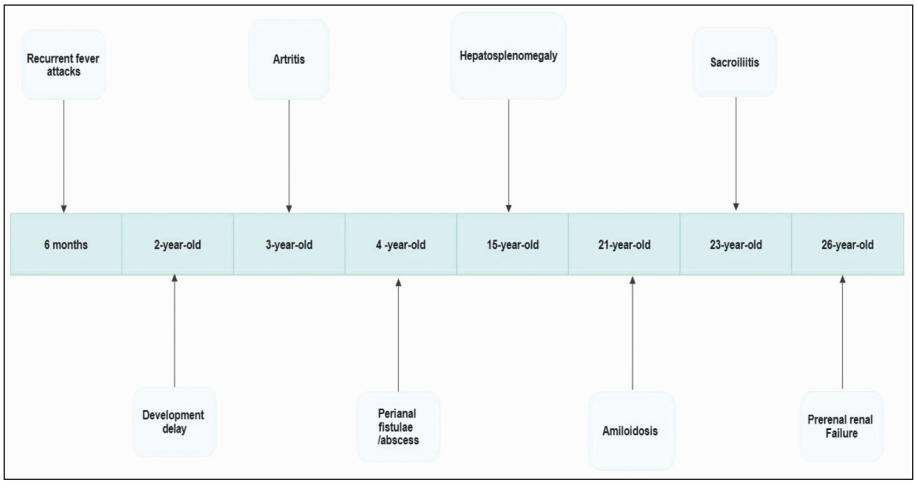

FIGURE 1: Clinical presentations of the patient by ages.

TABLE 1: Laboratory findings of the patient following colchicine and canakinumab treatments.

	After NSAID	After colchicine (At the age of 20)	After canakinumab (At the age of 22)
ESR (mm/h)	120	97	38
Fibrinogen (mg/dL)	594	413	399
SAA (mg/dL)	234	214	158
IgA level (mg/dL)	954 (96-465)	874 (139-378)	416 (139-378)

NSAID: Nonsteroidal anti-inflammatory drugs; ESR: Erythrocyte sedimentation rate; SAA: Serum amyloid A; Ig: Immunoglobulin.

She has been continuing to receive canakinumab for two years and her inflammatory symptoms have resolved. No side effects were observed.

Informed consent was taken from the patient.

DISCUSSION

MKD is a spectrum of disease that can differ from milder symptoms to severe, even life-threatening complications. Gastrointestinal findings such as abdominal pain, vomiting, and diarrhea can be seen during attacks in the most of the patients, mimicking inflammatory bowel disease (IBD), but severe gastrointestinal involvement is rare. Severe gastrointestinal involvement, perianal or gastrointestinal ulcers have been reported in 4% of patients with MKD in the Eurofever Registry.[3]

MKD is caused by the mutations in the gene encoding mevalonate kinase (MVK) which is involved in the cholesterol biosynthesis pathway.[4] Most cases with MKD have compound heterozygotes for missense mutations. The pVal377I and the plLe268Thr mutations are the most common mutations among patients with MKD.[5-7] The pV377I mutation was often related to continuous disease course, severe musculoskeletal involvement, gastrointestinal problems such as perianal ulcer, and fistulas.[8] We detected a heterozygous pVal377 mutation and a mutation p. Gly18Arg in the genetic analysis of our patient. Next generation sequencing revealed heterozygosity for the common c.1129G>A (p.V377I) and a. Gly 18Arg (c.52G>A) mutation in the *MVK* gene in our case. This is the fourth reported case with the same mutations and all of these cases are originally from Türkiye.[5]

The mutations that led to IBD in MVK deficiency were given in Table 2 with the clinical data in the literature.

Elevated interleukin-1 (IL-1) and IL-6 production have been suspected in the pathogenesis of diversity of autoimmune and inflammatory conditions.[6] A subgroup of patients has been treated with corticosteroids which reduced the severity of MKD episodes. Colchicine, NSAIDs, statins, and cyclosporine have been used with inadequate clinical responses.[1] The effect of anti-tumor necrosis factor alpha treatment in decreasing the frequency and duration of typical MKD attacks is controversial. IL-1 blockade has been determined as an effective treatment of many symptoms of MVK deficiency, including fever attacks and gastrointestinal inflammation.[1] Bianco et al. published six patients of early-onset IBD with both homozygous and heterozygous MVK mutations and considered that these

TABLE 2: MVK mutations with severe gastrointestinal involvements.

Genotype	Clinical presentations	Authors (reference no)
P. **Val377Ile**	Inflammatory colitis	Dunn et al.[10]
	Recurrent perianal abscess	Kisla Ekinci et al.[11]
		Our case
P. Leu6Glyfs*16	Inflammatory colitis	D'Osualdo et al.[9]
P. **Val132Ile**	Inflammatory colitis	Bianco et al.[7]
P. **ILe268Thr**	Inflammatory colitis	Dunn et al.[10]
	Recurrent perianal abscess	
P. L70Gfs*9	Recurrent perianal abscess	Kisla Ekinci et al.[11]
P. **Tyr116His**	Severe inflammatory colitis	Levy et al.[12]
P. **Ser135Leu**	Inflammatory colitis	D'Osualdo et al.[9]
P. **Gly326Arg**	Early-onset severe ulcerative colitis	Cuisset et al.[13]
P. **Gly339Ser**	Inflammatory colitis	Frenkel et al.[14]
	Perianal abscess	

MVK: Mevalonate kinase.

mutations could synergistically enhance the risk of bowel inflammation.[7] Our patient suffered from recurrent perianal fistulas from 4 years old to 22 years and successfully treated with monthly canakunimab treatment.

Renal amyloidosis is one of the long-term complication of certain autoinflammatory diseases.[8] Our case developed renal amyloidosis and prerenal renal failure due to very frequent attacks of inflammation. In a cohort, 5 out of 114 patients with MVK deficiency developed renal amyloidosis.[3] Kidney transplantation was performed in four due to end-stage kidney failure.

Sacroiliitis in MKD is extremely rare. There is only one case presenting MKD and sacroiliitis in the literature.[6] According to our knowledge, our case is the second case presenting with sacroiliitis.

Inflammatory colitis and perianal abscess or fistulas may be a part of autoinflammatory colitis in patients with MKD. Few reports pointed to a relation between MKD and perianal fistulas.[9,10]

In conclusion, MA manifests heterogeneous clinical symptoms and clinicians should keep in mind MKD in patients with a history of recurrent fever, high levels of inflammation markers, and perianal fistulas/abscess. Early recognition and treatment is important to prevent or reduce future irreversible damages.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sara Şebnem Kılıç;* ***Design:*** *Sara Şebnem Kılıç;* ***Control/Supervision:*** *Sara Şebnem Kılıç;* ***Data Collection and/or Processing:*** *Şükrü Çekiç, Şehime Gülsün Temel, Şebnem Özemri Sağ, Sara Şebnem Kılıç;* ***Analysis and/or Interpretation:*** *Sara Şebnem Kılıç,* ***Literature Review:*** *Hülya Köse;* ***Writing the Article:*** *Hülya Köse;* ***Critical Review:*** *Sara Şebnem Kılıç;* ***References and Fundings:*** *Hülya Köse;* ***Materials:*** *Hülya Köse.*

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