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Case report

A possibly new autoinflammatory disease due to compound heterozygous phosphomevalonate kinase gene mutation

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SUMMARY

Background: Mevalonate kinase (MVK) plays a role in cholesterol and non-sterol isoprenoid biosynthesis and its deficiency-related diseases are caused by bi-allelic pathogenic mutations in the MVK gene, (*MVK*), which leads to rare hereditary autoinflammatory diseases. The disease may manifest different clinical phenotypes depending on the degree of the deficiency in the enzyme activity. The complete deficiency of the enzyme activity results in the severe metabolic disease called mevalonic aciduria, while a partial deficiency results in a broad spectrum of clinical presentations called hyper-immunoglobulin D syndrome (HIDS). Serum immunoglobulin (Ig) D and urine mevalonic acid levels may be increased during inflammatory attacks of HIDS.
Case Presentation: Herein, for the first time in the literature, we present a 6-year-old male patient who suffered from recurrent episodes of fever, polyarthritis, skin rash, diarrhea, abdominal pain, and inflammatory bowel disease-like manifestations with elevated levels of serum IgD, and urine mevalonic acid. Eventually we detected compound heterozygous mutations in the phosphomevalonate kinase (*PMVK*) gene coding the second enzyme after mevalonate kinase in the mevalonate pathway.
Conclusion: For patients presenting with HIDS-like findings, disease exacerbations and persistent chronic inflammation, and having high urinary mevalonic acid and serum IgD levels, raising suspicion in terms of MVK deficiency (MVKD), it is recommended to study all mevalonate pathway enzymes, even if there is no mutation in the *MVK* gene. It should be kept in mind that novel mutations might be seen such as *PMVK* gene.

1. Introduction

Mevalonate kinase deficiency (MVKD) is an autosomal recessively inherited autoinflammatory metabolic disease, has three distinct clinical phenotypes, namely hyper IgD syndrome (HIDS), mevalonic aciduria (MA) and disseminated superficial actinic porokeratosis (DSAP) [1,2]. HIDS is characterized by attacks of fever, joint pain, lymphadenopathy, gastrointestinal symptoms, mucosal ulcers, and skin rash that usually begin in the first year of life due to partial deficiency of the MVK enzyme. Patients with MA have less than 1% of enzyme activity and may have ocular involvement, neurological symptoms, psychomotor developmental delay, cerebellar ataxia, prenatal and postnatal growth retardation, and atypical facial appearance [3,4]. DSAP, a recently described phenotype, is limited to the skin and significantly different from systemic disease [5].

Serum acute phase reactants, IgD, and urinary mevalonic acid levels usually increase during the inflammatory attacks in patients with MVKD [1]. The bi-allelic pathogenic variant of the *MVK* gene causes deficiency of MVK enzyme activity which plays a key role in the mevalonate pathway that results in elevated cholesterol, steroid, and bile acids [1,3]. In MVKD, accumulation of mevalonic acid reduces generation of downstream geranyl-geranyl-pyrophosphate (GGPP) which causes defective posttranslasyonel protein prenylation (Fig. 1) [1,6]. Inactivation of RhoA GTPase, the serine- threonine kinases protein kinase N1 (PKN1) and PKN2 develop due to defective prenylation, this leads to impeding the activation of inflammasome because of binding

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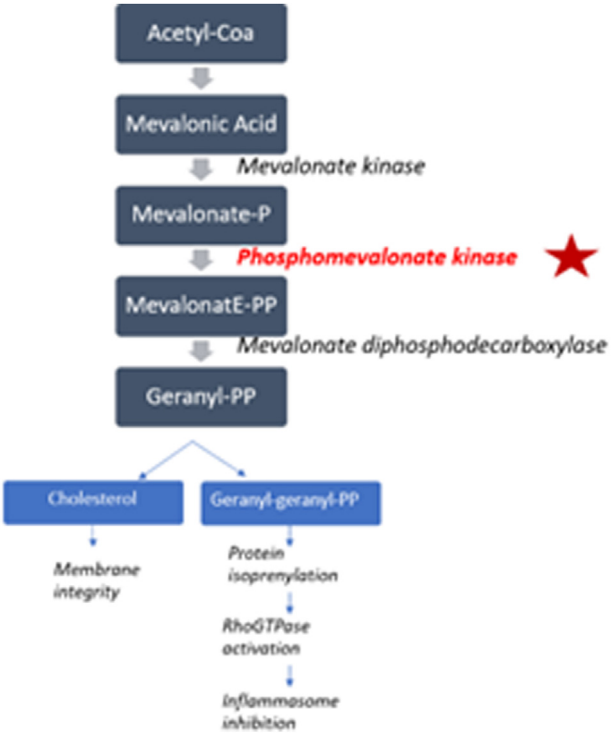

Fig. 1. Mevalonate kinase pathway.

and phosphorylation of pyrin by these specific kinases. In inflammasomes, the excessive production of proinflammatory cytokines, interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α), is responsible for the inflammatory systemic disease in MVKD [1,3]. Phospho-mevalonate kinase (PMVK) enzyme is the next enzyme to the MVK enzyme in the mevalonate pathway [1,3]. There are no reports related to the development of auto-inflammatory diseases due to PMVK deficiency in the current literature.

Herein, for the first time in the literature, we present a pediatric patient who suffered from recurrent fever attacks with diarrhea, abdominal pain, polyarthritis, skin rash, and inflammatory bowel disease without any mutations in the *MVK* gene but with a compound heterozygous mutation in the *PMVK* gene in the mevalonate pathway.

2. Methods

Gas chromatography–mass spectrometry method was used for urine organic acid analysis, and next generation DNA sequencing was used for *PMVK* gene analysis. Written informed consent was obtained from the participant.

2.1. Case presentation

A 6-year-old male patient was admitted with prolonged fever, cryptic tonsillitis, cervical adenitis, conjunctivitis, edema on hands and feet, maculopapular skin rash, and desquamation in the genital area. In laboratory work-up, high levels of acute phase reactants were detected. Initially, a diagnosis of Kawasaki disease was made and intravenous immunoglobulin with acetylsalicylic acid was administered. In his medical history, the first degree of parental consanguinity, and recurrent attacks of fever, diarrhea, abdominal pain, and arthritis were remarkable. Immunodeficiency-related diseases were excluded. Antinuclear antibody, anti dsDNA, antineutrophil cytoplasmic antibody, and rheumatoid factor were negative, and serum complement levels were normal. Colchicine treatment was initiated due to the clinical diagnosis of familial Mediterranean fever (FMF) despite no *MEFV* gene mutation. As the attacks of the patient were partially alleviated and acute phase reactants were relatively subsided, colchicine treatment was continued. In the fourth year of the treatment, due to the development of arthritis in the left knee and ankle lasting longer than six weeks, a diagnosis was made as oligoarticular juvenile idiopathic arthritis accompanied by FMF; non-steroidal-anti-inflammatory drug (NSAID), corticosteroid, and methotrexate treatments were initiated. Because of persistent arthritis, etanercept was added. Over an 8-year period, he continued to have arthritis, sustained high acute phase reactants, and fluctuating gastrointestinal symptoms which became evident in the 4th year of his admission. He was unresponsive to different immunosuppressive treatments, including anti-TNF (adalimumab, etanercept), anti-IL-6, anti-IL-1, corticosteroid, methotrexate, and azathioprine (Fig. 2). Additionally, due to the chronic sustained inflammation he had a significant growth retardation (height SDS: < −3), clubbing and extensive verruca vulgaris on his hands, feet, and facial area, resistant to local cryotherapy, lasting more than two years. Ustekinumab therapy which is a monoclonal antibody to IL-12/23, is planned to initiate to the patient. During the follow-up, due to the detection of high IgD levels (IgD: 200 mg/dL (N:0–100)) and the increased excretion of mevalonic acid in urine organic acid analysis, *MVK* gene analysis was performed and found negative. Whole exome sequencing revealed compound heterozygous c.329G > A (p. Arg110Gln) and c.316G > A (p. Val106Met) mutations in trans configuration in the *PMVK* gene (NM_006556.4) coding phosphomevalonate kinase enzyme (Fig S1) [See the supplementary material associated with this article online] [7]. The c.329G > A mutation was classified as "Likely pathogenic (allele frequency: 0.000164) and the novel c.316G > A mutation was classified as "Variant of unknown significance" (allele frequency: 0) according to American college of

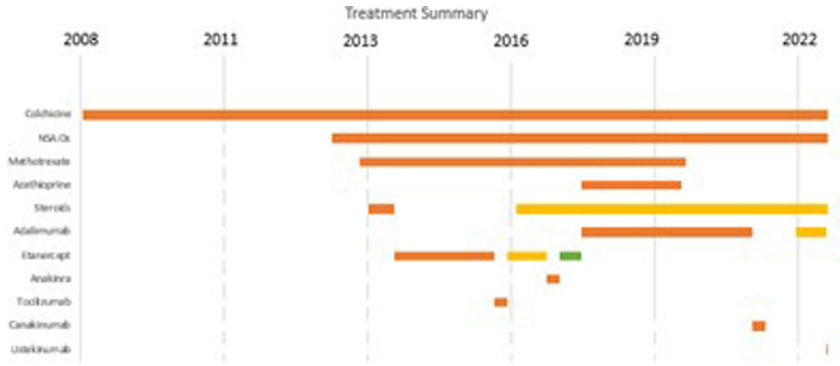

Fig. 2. Treatment summary of the patient.

Medical Genetics Classification [8]. The functional studies are still being conducted to show the pathophysiologic link.

3. Discussion

To our knowledge, this is the first case in the literature with a clinical spectrum of mevalonic aciduria-HIDS, which probably occurs due to PMVK enzyme deficiency due to compound heterozygous *PMVK* gene mutations and is a candidate for a newly identified disease.

Many phenotypes have been associated with pathogenic variants in the *MVK* gene, all of which are a heterogeneous group defined as auto-inflammatory diseases [1]. Although the pathophysiology of MVKD is more clear day by day, the phenotype-genotype correlation has not been fully elucidated yet [6]. A wide spectrum of cases including neonatal-onset ulcerative colitis, cyclic neutropenia, macrophage activation syndrome, retinitis pigmentosa, DSAP, hidradenitis suppurativa, and granulomatous uveitis have been reported [1–3]. Atzmony et al. has reported a germline-heterozygous *PMVK* c.329 > A mutation in association with linear porokeratosis [9]. Additionally, there are variants of MVKD with typical or milder attacks, despite decreased MVK activity. Comprehension of the fact that MVK-related diseases caused by decreased enzyme activity may accelerate the discovery of targeted therapies and promising developments for the future [1].

Pathogenic variants of the *MVK* gene inhibit the folding and stability of MVK, hence its enzymatic activity, resulting in mevalonic acid accumulation, decreased GGPP production, and defective prenylation [1,3]. The mutations in the *PMVK* gene in our patient probably resulted in the deficiency of the enzyme that is involved in the next step in the same pathway, and we envision that it may cause the clinical picture of our patient, who has features similar to and differing from MVK deficiency disease spectrum. Jeyaratnam et al. evaluated 61 pediatric patients who had two pathogenic variants on the *MVK* gene or had decreased activity of the MVK enzyme. 48 patients did not have any *MVK* gene mutation but 5 of them had elevated urine mevalonic acid levels with recurrent febrile attacks, these patients could not be diagnosed with a final diagnosis. In this study, the specificity and sensitivity of increased mevalonic acid levels in HIDS/MVKD patients have been reported as 92% and 90%, respectively [10]. Although the elevation in serum IgD levels has low diagnostic sensitivity and specificity [11], it was considered clinically significant when the increased urinary mevalonic acid and serum IgD levels detected in our patient were evaluated together.

NSAIDs can help to relieve symptoms during inflammatory attacks, and short-term use of corticosteroids may be effective to alleviate the inflammatory attacks. Anti-IL-1 therapies may be effective for terminating inflammatory attacks and should be considered to limit and prevent the side effects of steroids. Anti-IL-6 and anti-TNF-α therapies can also be used in cases with frequent attacks or with ongoing subclinical inflammation [2,3]. Allogeneic hematopoietic stem cell transplantation is a treatment option in severe cases resistant to available medical treatments [11]. However, since it has its own risks, it should be evaluated on a case-by-case basis and pros and cons should be weighed [12]. Our patient was unresponsive to anti-IL-1 therapy, partially responded to anti-TNF-α therapy, and was unresponsive to anti-IL-6 therapy which was initiated due to the persistence of subclinical inflammation. As the patient had Crohn's disease-like findings, peripheral polyarthritis, and persistent clinical and laboratory findings of inflammation, it is considered that he might respond to ustekinumab therapy. He did not have a mutation in the *MVK* gene, but compound heterozygous mutations in the *PMVK* gene in the whole exome sequencing. Although we think that this enzyme, which provides the main substrate but takes part in the next step, may be responsible for our patient's clinical findings, further studies are needed to elucidate this relationship. A functional study of mutant PMVK activity is still being conducted, and if PMVK deficiency is clearly shown to be responsible for the pathogenesis after functional studies, it may become a candidate for a targeted therapy.

In conclusion, for patients presenting with HIDS-like findings, disease exacerbations and persistent chronic inflammation, and having high urinary mevalonic acid and serum IgD levels but without a MVK gene mutation, it is recommended to study all mevalonate pathway enzymes to identify a novel gene as PMVK gene.

Disclosure of interest

The authors declare that they have no competing interest.

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Data availability

Data sharing is not applicable–no new data is generated, or the article describes entirely case report.

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Online Supplement. Supplementary data

Supplementary data (Figure S1) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2022.105490.

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