Annals of Case Reports & Reviews

Case Report

doi: 10.39127/2574-5747/ACRR:1000225
Morabito LA, et al. Annal Cas Rep Rev: ACRR-225

Overlap Between Mevalonate Kinase Deficiency and Familial Mediterranean Fever: Case Report and Review of Literature

Letteria Anna Morabito[1], Diana Sutera[1], Anna Maria Bagnato[1], Alessandra Spagnolo[1], Francesca Mazza[1], Romina Gallizzi[2]*

[1]Department of Human Pathology of Adulthood and Childhood Gaetano Barresi, University of Messina, Messina, Italy
[2]Pediatric Unit, Department of Medical of Health Sciences, Magna Graecia University, Catanzaro, Italy

***Corresponding author:** Romina Gallizzi. Pediatric Unit, Department of Medical of Health Sciences, Magna Graecia University Catanzaro, Italy. Viale Europa 88100 Catanzaro, Italy. Tel: 3474341001. E-mail: rgallizzi@unicz.it

Citation: Morabito LA, Sutera D, Bagnato AM, Spagnolo A, Mazza F, Gallizzi R (2021) Overlap Between Mevalonate Kinase Deficiency and Familial Mediterranean Fever: Case Report and Review of Literature. Annal Cas Rep Rev: ACRR-225.

Received Date: 09 April 2021; **Accepted Date:** 15 April 2021; **Published Date:** 23 April 2021

Abstract

Background: *Autoinflammatory diseases represent a large group of conditions characterized by mutation of genes codifying for proteins with a key role in the regulation of inflammatory process. In the last 20 years, thanks to the improvement in diagnostic tests and the advent of new genetic techniques (Next-generation sequencing-NGS- and exome analysis), unknown pathogenetic mutations and co-existence of different autoinflammatory syndromes specific mutation in the same subject have been discovered.*

Methods: *We describe the case of a 16- years-old young girl with a history of recurrent episodes of fever since infancy. Genetic testing revealed a condition of compound heterozygosis for the common V377I Mevalonate kinase (MVK) gene mutation and the rare P228L variant. Specific sequencing for MEFV (Mediterranean Fever) gene also revealed the presence of V726A heterozygous mutation.*

Results: *Our patient's clinical picture was atypical for both the diseases because of the presence of recurrent and long-duration feverish episodes, in association with right sacroileitis, episodes of facial nerve palsy during bouts and pubertal delay. The start of TNF-α blocker treatment showed a remarkable clinical improvement, with the resolution both of fever and sacroileitis and a significant change in clinical phenotype after the discontinuation of therapy.*

Conclusions: *The presence of more than one mutation in different genes of monogenic autoinflammatory diseases in the same individual might be responsible for atypical clinical manifestations with overlap features of both the syndromes and explain different treatment response and changes in clinical phenotype. Our case report, similarly to other previous works, underline the importance to research the presence of mutations involving genes responsible for other AIDs in patients affected by one autoinflammatory disease with atypical clinical features and poor response to conventional treatment.*

Keywords: *mevalonate kinase deficiency, familial mediterranean fever, overlap syndrome, TNF-α blocker treatment.*

Introduction

Autoinflammatory diseases (AIDs) are a group of conditions characterized by recurrent flares of systemic inflammation. They generally start with sudden feverish episodes, associated with increased levels of acute phase reactants, and with a different number of clinical manifestations such as cutaneous rash, serositis (peritonitis, pleurisy, pericarditis), lymphadenopathy and arthritis.

Most autoinflammatory diseases are caused by the dysregulation of innate immune system, in absence of significant levels of antibodies or antigen-specific T cells. Symptom-free intervals are characterized by complete wellbeing, normal growth and complete normalization of acute phase reactants [1,2].

Familial Mediterranean Fever (FMF) is the most common monogenic AID. It is an autosomal recessive disease, determined by the mutation of MEFV gene located on chromosome 16 (p13.3) codifying a protein called pyrin, which is a part of inflammosome complex. The syndrome usually begins before the age of ten, but also an adult onset has been observed.

Attacks are irregular, unpredictable in frequency, usually unprovoked and they are characterized by recurrent episodes of fever, typically lasting for 1–3 days. Fever is often accompanied by serositis (pleurisy, peritonitis,

pericarditis), erysipela-like rash over the lower limbs or arthritis [3].

Colchicine treatment is effective in preventing bouts and amyloidosis. In non-responder patients anti Interleukin 1 (anti IL-1) drugs are an alternative therapeutic strategy [4].

Mevalonate Kinase Deficiency (MKD) or Hyper IgD Syndrome (HIDS) or Netherland fever is a very rare autoinflammatory disease, with an autosomal recessive transmission. Mutations of MVK gene, located on chromosome 12 (12q24), impair the function of mevalonate kinase enzyme, a key-molecule of cholesterol and isoprenoids pathway, and cause the syndrome through an indirect activation of the inflammasomes and the hypersecretion of IL-1.

Clinical picture of MKD is characterized by recurrent febrile episodes lasting 4 to 6 days, laterocervical lymphadenopathy, abdominal pain and change in bowel habits with vomiting.

Non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine therapy are not useful to solve symptoms, instead of steroid therapy. Nowadays, lots of clinical and literature data show the effectiveness of treatment both with anti-IL-1 and anti-TNF alpha agents. However, it isn't possible to recommend one rather than the other for lack of a certain data regarding the comparison between them [5].

During the last years, thanks to new emerging tools, such as Next Generation Sequencing (NGS), more and more cases of mutations involving different AIDs genes have been discovered.

Clinical features of these combinations are unclear. Multiple variations in AIDs genes could occur in the same patient and potentially influence the clinical presentation (atypical or overlap clinical frameworks) and the response to treatment [6-7].

We describe the case of a 16 year-old-girl who was diagnosed with MKD (V377I/P228L), in association with a heterozygous mutation for FMF (V726A).

Materials and Methods

We report the case of a 16 year-old-girl, who presented a history of recurrent fever episodes starting at the age of 8 months. Every episode lasted for 10-15 days and was characterized by fever, preceded by chills, oral aphtosis, erithemato-papular rash, general malaise, cervical lymphoadenopathy, abdominal pain and diarrhoea.

The attacks occurred monthly, with a variable of free intervals, during which the girl felt better. Disease recurrence continued despite tonsillectomy, adenoidectomy and appendectomy.

At the age of 14, the onset of inflammatory low back pain and arthritis of limbs great joints were registered during fever attacks, in association with recurrent episodes of headache. Differently from previous attacks, the feverish cutaneous rash disappeared and never presented itself again.

From 6 to 16 years of age, she also presented four episodes of facial nerve palsy during bouts. She came to our attention at the age of 16 during one of these feverish episodes. She was in poor general conditions. Clinical examination revealed the presence of splenomegaly and generalized lymphoadenopathy. A severe growth delay (weight under 5th centile, height under 10th centile), delayed puberty and primary amenorrhea were present. Laboratory data showed a significant increase in acute phase reactants, neutrophilic leukocytosis and microcytic anemia, whereas instrumental investigations highlighted the presence of right sacroileitis.

Results

We suspected the presence of an autoinflammatory disease, in particular we carried out specific genetic tests for MKD and TRAPS (Tumor necrosis factor receptor-associated periodic syndrome) because of the duration of fever attacks; moreover, in view of the girl's origin, we performed FMF genetical testing. She was in fact from the South of Italy (Sicily), where this disease has a high prevalence [8].

Genetic testing showed a well-described missense mutation in exon 11 (V377I) and a new missense mutation in exon 8 (c.683 C>T, p.P228L) of MVK gene. Biochemical investigations of lymphocytes revealed the markedly reduced activity of MVK (7 pmol/min/mg, control 142 pmol/min/mg), so diagnosis was confirmed.

It was also found a MEFV mutation in exon 2 (c. 2177 C>T, p.V726A) in a heterozygous state. V377I MVK and V726A MEFV gene heterozygous mutations were transmitted by her father and the new variant P228L was found in her mother. Both the parents were asymptomatic.

Colchicine treatment was started, but it resulted uneffective, so she was treated with prednisone (2mg/kg) with a good clinical response. Steroid treatment was subsequently suspended because of the high number of fever attacks and the high necessary doses.

At the age of 21 she started biologic agent's treatment with anti-tumor necrosis factor alpha (Adalimumab), that induced clinical remission without flares, appearance of the menarche, improved her nutritional status and quality of life.

Features	FMF	MKD	Our patient (Overlap syndrome)
Duration of fever attacks	6- 72 hours	3-7 days	7-10 days
Free interval duration	Irregular (from 1 week to several months or even years)	2 to 8 weeks	2 weeks
Age of onset	Within the first decades of life. (Rare beginning after the age of 40)	First week of life - 20 years (first year of life, and before the age of 5 for the vast majority of the patients)	8th month of life
Main Clinical Features	Fever Serositis: - Peritonitis (abdominal pain, often confused with acute abdomen, constipation or diarrhea, vomiting) - Pleuritis and pericarditis (chest pain, dyspnea, ST segment anormality on ECG, tamponade and rare constructive pericarditis) - Orchitis (scrotal edema, due to inflammation of the tunica vaginalis)	Fever Abdominal pain Diarrhea Vomiting	Fever Abdominal pain Diarrhea
Muscoloskeletal symptoms	Arthralgia Arthritis (large joints of lower extremities) 3 forms: 1. asymmetric, non destructive arthritis 2. chronic destructive arthritis 3. poliarticular joint involvement Myalgia	Arthralgia Arthritis (mainly in large peripheral joints) Myalgia	Arthritis of limbs great joints Right sacroileitis
Cutaneous and mucocutaneous symptoms	Erysipelas-like erythema (ankle, leg extensor site surface)	Maculopapular rash Aphthous ulcers (or stomatitis) Pharyngitis	Erithemato-papular rash Oral aphtosis
Lymphoid tissue symptoms	Hepatomegaly Splenomegaly	Lymphadenopathy (mainly in the cervical region) Splenomegaly	Generalized lymphoadenopathy. Splenomegaly
Other symptoms	Discomfort Irritability Aseptic meningitis	Headache Cold chills Malaise Fatigue	Headache during fever Chills General malaise Facial nerve palsy
Growth	Normal	Normal or delay	Severe growth delay Pubertal delay Primary amenorrhea

Laboratory findings	Increased acute phase reactants Increased levels of serum SAA Mild leucocytosis Normocromic normocytic anemia	Elevated concentrations of serum IgD and IgA Strong acute-phase reactants increase Elevated white blood cells count Pro-inflammatory cytokines (such as IL-1β and IL-6) increase Elevated urinary mevalonic acid concentrations	Elevated acute phase reactants Neutrophilic leukocytosis Microcytic anemia
Response to colchicine	Yes	No	No
Steroidal treatment response	Not used	Partial or complete response	Complete response
Biological agents	Efficacy of Anakinra/ Canakinumab in colchicine resistant patients	Partial/complete response to • Anakinra / Canakinumab • Etanercept	Complete response to Adalimumab
Amyloidosis risk	High risk if not treated	3% frequency	Not observed

Table 1: Comparison among FMF, MKD and overlap syndrome features

Adalimumab therapy was suspended after 4 years because the patient took the decision to undergo a pregnancy. Her pregnancy ran without bouts and she gave birth to a female child to this day enjoys good health. After pregnancy no therapy was required to control the disease and also the patient's clinical phenotype changed: she presented only a few attacks per year, associated to more attenuated signs and symptoms than before and she needed only short cycles of steroid therapy.

Discussion

We described a case report concerning a genetic overlap between MKD and FMF, characterized by the coexistence of compound heterozygosis of MVK gene (P228L/V377I) and a MEFV mutation (V726A), and atypical clinical features for both the syndromes.

Our patient presented very long fever attacks (in spite of 4-6 days of the typical form of MKD) and an articular axial involvement, that isn't usually present in MKD, but was already described in FMF. Other atypical manifestations were the presence of cranial nerve palsy, that was neither described in MKD or FMF patients, and growth and pubertal delay [9]. According to literature data, patients with AIDs usually showed a normal growth.

Another feature was the poor response to colchicine therapy, that was indicated for FMF first line treatment, but uneffective in MKD patients.

Simultaneous presence of mutations in MEFV and MVK genes segregating in the same subject and also among members of his own family were already described in literature with truly variable clinical implications, but no one showed a modified clinical phenotype after biological medications, as observed in our patient.

First description of a patient with combined MKD and FMF had been made in 2014 by Chandrakasan et al. [10] that reported the case of a girl with a history of prolonged episodes of fever, maculopapular rash, abdominal pain and diarrhea, with mild growth and developmental delay since infancy, like our previous description. Symptom-free intervals were very short (few days), instead of the classical pattern of MKD that is typically longer (weeks).

Genetic testing revealed p.I268T/p.V377I compound heterozygous mutations in MVK gene and a concomitant p.E230K/-MEFV variant. Moreover, similarly to our patient, the girl had inherited all these mutations from her parents, both asymptomatic.

The mother was heterozygotes for p.I268T MVK mutation and the father was heterozygotes for p.V377I MVK mutation and p.E230K MEFV variant. She well responded to combination of colchicine and prednisone.

Other two cases of FMF and MKD overlap were also described in 2014 [6]. Patients were a brother and a sister, with a history of periodic fever, associated with several symptoms and elevated acute phase reactants levels. Both of them presented a condition of homozygous for p. V377I mutation in MVK. The girl also presented a compound heterozygosis for p.E148Q/p.P369S/p.R408G and p.E167D/p.F479L for MEFV gene and, since she was 8, she presented episodes of fever (39–40°C), abdominal pain and arthralgia lasting 3 – 5 days every 3-4 weeks.

The starting of colchicine treatment allowed to obtain a good control of disease. The older brother, who also presented a condition of compound heterozygosis for p. E148Q/p.P369S/p.R408G and p.M680I mutation in MEFV gene, had a worse phenotype because of an earlier clinical onset of the symptoms (at the age of 8 months) , characterized by episodes of periodic fever associated with abdominal pain, vomiting, diarrhea, cervical lymphadenopathy and severe arthritis every 3 weeks and later became every 3-4 months.

He was treated with colchicine up to 2 mg daily associated with naproxen, with poor response and then he discontinued medications after 4 years.

After puberty, episodes became less frequent and mild for 5 years. Later, at the age of 17, he developed shorter episodes of fever and abdominal pain, without rash or lymphadenopathy. He restarted gradually colchicine treatment up to 0.5 mg twice/daily with and the episodes became less frequent and less severe. He also required short courses of oral prednisone 0.5–1 mg/kg daily for 5–7 days during episodes.

Interestingly, other genetically affected family members, who were all homozigotes for p.V377I mutation in MVK and with two MEFV complex alleles, were asymptomatic (like a 14-years-old sister) or had less symptoms (two brothers, with rare episodes of fever associated with cervical lymphadenitis).

All these cases demonstrated that simultaneous presence of mutations involving more than one gene of monogenic autoinflammatory disorders were associated with a "mixed" phenotype, in which we could find intermediate or atypical clinical features of both the diseases and a different pattern of response to treatment. For example, three of the four reported patients presented a little or a poor response to colchicine, which is usually not effective in MKD albeit it was combined with prednisone [10].

Another case report recently described is that of a 10-year-old Spanish boy of consanguineous parents (cousins) who was diagnosed with MVK (p.V377I homozygous) and overlap with p.148Q mutation in homozygous for FMF. He showed good clinical response to canakinumab after refractoriness with other treatments (no response to colchicine, Anakinra and Methotrexate, partial clinical response to Etanercept). His symptoms started since he was four months old every 2–8 weeks with episodes of fever lasting 3 days, accompanied by oral aphthae, abdominal pain and emesis [11].

A work published in 2016, showed a molecular connection between FMF and MKD, even if these disorders appeared different. This link could explicate the lack of efficacy of colchicine treatment in most of the patient with this overlap conditions.

Colchicine explicates its therapeutical effect activating a protein G- complex, called RhoA, that has a key role in inhibiting IL-1 release from inflammosome complex activated by pyrin [12].

When mutations of MEFV gene are present, RhoA activity is blocked and IL-1 release results free from inhibitions. Colchicine treatment is effective in FMF patients because it promotes the release of RhoA activators from microtubules and restore this control mechanism.

In MKD patients, colchicine is not effective because RhoA activity is blocked upstream: MVK mutation prevents RhoA geranylgeranylation, a very important stage to allow the translocation of this protein from citosol to plasma membrane, where it plays its inhibitory function.

Geranylgeranyl pyrophosphate, that is the substrate of this process, is a product of mevalonate pathway. Mutation of MVK, that is typical of MKD, blocks this process and also stops next events including the inhibition of IL-1 beta release [13].

If we consider that cytokine activation is the endpoint of inflammatory process, the use of anti-cytokines as a therapeutic option in MKD patients is useful, as demonstrated by the good response of our patient to adalimumab treatment.

In our case we reported the coexistence, in the same patient, of a well described V726A mutation of MEFV gene with two different mutations MVK gene, one of which (P228L) was new and poorly known. We could not say if this novel genotype was the only responsible of our patient's different clinical picture and response to treatment. Moreover, we were not sure if the presence of a MEFV gene mutation could modify clinical expressiveness of MKD or influence the natural history of this disease, as reported in previous literature works. For all these reasons, further studies should be performed in order to clarify the features of this overlap condition.

Conclusion

The presence of multiple mutations in AID genes in the same patient configures a condition of overlap syndrome and this could potentially influence clinical presentation and response to treatment.

Patients affected by one monogenic periodic fever with atypical or incomplete clinical features should be screened for the presence of mutations involving genes responsible of other AIDs, even in presence of a negative family history. This strategy, in fact, could be useful in order to develop more effective and tailored therapeutic strategies.

Funding: Not applicable

References

1. Federici S, Caorsi R, Gattorno M. The autoinflammatory diseases. Swiss Med Wkly. 2012. 19;142:w13602 (https://pubmed.ncbi.nlm.nih.gov/22714396/).
2. Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol. 2009. 27:621-68 (https://pubmed.ncbi.nlm.nih.gov/19302049/).
3. Kucuk A, Gezer IA, Ucar R, Karahan AY, Familial Mediterranean Fever. Acta Medica (Hradec Kralove). 2014. 57(3):97-104 8 (https://pubmed.ncbi.nlm.nih.gov/25649364/).
4. Cetin P, Sari I, Sozeri B, Cam O, Birlik M, Akkoc N, et al. Efficacy of interleukin-1 targeting treatments in patients with familial mediterranean Fever. Inflammation. 2015. 38(1):27-31 (https://pubmed.ncbi.nlm.nih.gov/25139580/).

5. Javier LA, Schulert GS, Mevalonate kinase deficiency: current perspectives. Appl Clin Genet. 2016. 20(9):101-10 (https://pubmed.ncbi.nlm.nih.gov/27499643/).
6. Moussa T, Aladbe B, Taha RZ, Remmers, EF, El-Shanti H, Fathalla BM, Overlap of Familial Mediterranean Fever and Hyper-IgD Syndrome in an Arabic Kindred. J Clin Immunol. 2014. 35(3): 249-53 (https://pubmed.ncbi.nlm.nih.gov/25708585/).
7. Hoang TK, Albert DA, Novel presentations of periodic fever syndromes: Discrepancies between genetic and clinical diagnoses. Eur J Rheumatol. 2019 Jan;6(1):12-8; doi: 10.5152/eurjrheum.2018.18023. (https://pubmed.ncbi.nlm.nih.gov/30407166/).
8. La Regina M, Nucera G, Diaco M, Procopio A, Gasbarrini G, Notarnicola C, et al. Familial Mediterranean fever is no longer a rare disease in Italy. Eur J Hum Genet. 2003. 11(1):50-6. (https://pubmed.ncbi.nlm.nih.gov/12529705/).
9. Di Gangi M, Amato G, Converso G, Benenati A, Leonetti C, Borella E et al. Long-term efficacy of adalimumab in hyperimmunoglobulin D and periodic fever syndrome. Isr Med Assoc J. 2014. 16(10):605-7. (https://pubmed.ncbi.nlm.nih.gov/25438442/).
10. Hoffmann GF, Charpentier C, Mayatepek E, et al. Clinical and biochemical phenotype in 11 patients with mevalonic aciduria. Pediatrics 1993;91(5 I):915–21. (https://pubmed.ncbi.nlm.nih.gov/8386351/).
11. Chandrakasan S, Chiwane S, Adams M, Fathalla BM. Clinical and Genetic Profile of Children with Periodic Fever Syndromes from a Single Medical Center in South East Michigan. J Clin Immunol. 2014.34:104–113. (https://pubmed.ncbi.nlm.nih.gov/24233262/).
12. Flores Robles BJ, Peirò Callizo ME, Sanabria Sanchinel AA, Fernàndez Diaz C. Mevalonate kinase deficiency (hyper-IgD syndrome) overlap mutation familial Mediterranean fever. Reumatol Clin. 2017.13(1):57 (https://pubmed.ncbi.nlm.nih.gov/27079959/).
13. Hwan Park Y, Wood G, Kastner DL, Chae JJ. Pyrin Inflammasome Activation and RhoA Signaling in the Autoinflammatory Diseases FMF and HIDS. Nat Immunol. 2017. 17(8):914–21. (https://pubmed.ncbi.nlm.nih.gov/27270401/).
14. Zhang S, Natural history of mevalonate kinase deficiency: a literature review.Pediatric Rheumathology. 2016. 14:30. (https://pubmed.ncbi.nlm.nih.gov/27142780/).