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CASE REPORT

Mevalonate Kinase Deficiency as A Cause of Periodic Fever- A Report of Two Cases

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Abstract

Mevalonate kinase deficiency (MKD) is an exceedingly rare autosomal recessive inborn metabolism error characterized by mutations in the MVK gene, leading to impaired synthesis of cholesterol and isoprenoids. Two case reports of MKD in South India, shedding light on the disease's clinical heterogeneity are described here. The first case involves an eleven-month-old child with recurrent febrile attacks, joint pain, and a family history of similar complaints. In the second case, a 2-year-old born to consanguineous parents presents with severe manifestations, including joint deformities, developmental delay, and malnutrition.Exome sequencing confirmed the diagnosis, identifying specific mutations in the MVK gene.

Keywords:

Autosomal recessive, Mevalonate kinase deficiency, MVK gene mutations

Introduction

Mevalonate kinase deficiency (MKD) is an extremely rare autosomal recessive inborn error of metabolism. There have only been approximately 300 cases reported worldwide to this date[1]. This disease occurs due to mutations in the MVK gene, which encodes for an enzyme known as mevalonate kinase. The enzyme plays a key role in synthesizing cholesterol and isoprenoids, the deficiency of which forms the basis for this disease's pathogenesis. MKD has a wide clinical spectrum, ranging from a milder form known as Hyper IgD syndrome (HIDS) to the more severely manifested disease known as mevalonic aciduria[2]. The clinical picture in HIDS is similar to other periodic fever syndromes, characterized by recurrent febrile attacks, arthralgia, maculopapular rashes, etc.In contrast,mevalonic aciduria is much more detrimental and can cause mental impairment, facial dysmorphism, and growth retardation[3]. Very few cases of mevalonate kinase deficiency have been detected in India so far[4]. We hereby report two cases of mevalonate kinase deficiency from South India.

Case Presentation

History

Case 1: An eleven-month-old male child presented with high-grade fever associated with chills and a generalized rash over his body for ten days. Previous febrile attacks had been reported on prior vaccinations. The patient also had joint swelling and pain involving bilateral knees, elbows, and the right wrist (*Fig. 1, 2, 3*). A failure to thrive was noted in the child as well. His brother had similar complaints at three years of age and was treated as systemic juvenile idiopathic arthritis. Physical examination revealed axillary and cervical

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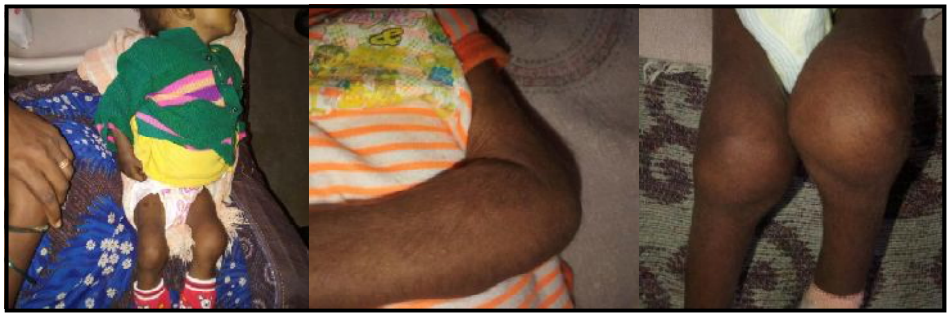

Fig. 1 and Fig. 3: Bilateral Knee Joint Swelling, Fig. 2: Left Elbow Joint Swelling

lymphadenopathy and splenomegaly.

Case 2: A 2-year-old male child, born of a 3rd-degree consanguineous marriage, presented with high-grade fever associated with chills for four days and a generalized rash over the body. He had a history of recurrent febrile attacks since 3 months of age. There was also joint swelling and pain since 3 months of age, involving bilateral knees, followed by elbows and ankles (*Fig. 4, 5, 6 7*). The development of joint deformity worsened this, and the child was unable to sit without support. A global developmental delay was noted in the child. His elder sibling was managed for similar complaints. Examination revealed frontal bossing and facial dysmorphism. Aphthous ulcers were noted in the oral cavity, and limb examination showed grossly deformed hands and digits. The patient was severely malnourished and had height and weight below three standard deviations for his age.

The results of investigations conducted in both cases were as displayed in *Table 1*.

Exome sequencing mutation c.1097A>G in exon 11 of MVK was detected, and the same mutation was found in the patient's elder brother. missense variant c.1162C>T in exon 11 of MVK was found, confirming our diagnosis.Exome sequencing clinched the diagnosis of mevalonate kinase deficiency in both patients. Both patients were treated with NSAIDs and steroids. However, the first child passed away before the genome sequencing test results were available, and the second patient was lost to follow-up.

Discussion

Mevalonate kinase deficiency (MKD) is an extremely rare autosomal recessive disorder with an estimated prevalence of 1-9 cases per million births worldwide.[2]

The recurrent febrile attacks noted in Case 1 are characteristic of HIDS, along with other accompanying features like lymphadenopathy, abdominal pain, diarrhea, and arthralgias.The joint involvement typically exhibits migratory non-erosive arthritis, mainly targeting large joints such as knees, ankles, and elbows. Case 2 exemplified a more severe end of the disease spectrum, with dysmorphism, developmental delay, and deformative arthropathy in keeping with mevalonic aciduria. The history of parental consanguinity and affected siblings also strongly supports an autosomal recessive inheritance.

Previously, Nienke M. ter Haar *et al.* conducted a study involving 114 MKD patients from the international Eurofever registry, providing key insights into the clinical and genetic characteristics of the largest MKD cohort examined. Patients, with a median onset age of 0.5 years experienced an average of 12 annual episodes featuring symptoms such as gastrointestinal issues, mucocutaneous involvement, lymphadenopathy, and musculoskeletal symptoms. [5]

Exome sequencing clinched both patients' diagnoses by identifying pathogenic variants in MVK exon 11. Over 150 mutations throughout the MVK gene have been implicated in MKD, with exon 11 mutations being the most frequent[6]. The specific mutation c.1097A>G found

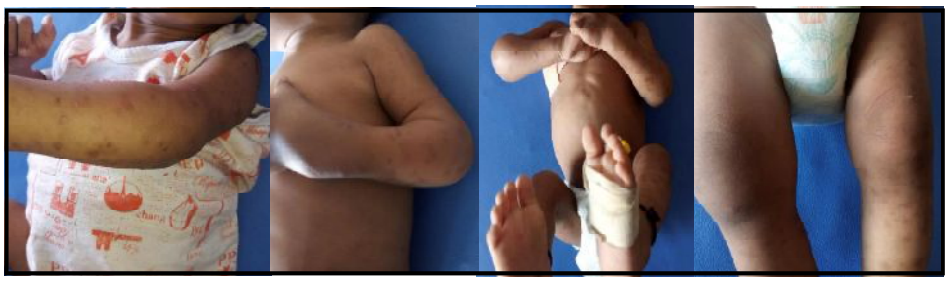

Fig. 4, 5, 6, 7: From left to right: Child with Bilateral Elbow, Wrist, and Knee Joint Swelling with Maculopapular Rashes

Table 1. Biochemical Investigations of Case 1&2

Investigation	Case 1	Case 2
Total leucocyte count (6000-17000/mm3)	21000	4000
Haemoglobin (11.3-14.1gm/dl)	8.8	6.0
C- Reactive Protein (<5mg/L)	54	48
Erythrocyte sedimentation rate (0-10 mm/hr)	105	130
Antinuclear antibody profile	Negative	Negative
Rheumatoid factor(<14.00IU/mL)	Negative	Negative
Serum IgA(30 – 120mg/dl)	Normal	Normal
SerumIgD (<or=10 mg/dL)	NA	NA
Ophthalmologic examination	Normal	Normal
Ultrasound abdomen	Splenomegaly	Splenomegaly
Ultrasound of knee joint	Synovial thickening	Synovial thickening
Exome sequencing	mutation **c.1097A>G** in exon 11 of MVK was detected, and the same mutation was found in the patient's elder brother.	missense variant **c.1162C>T** in exon 11 of MVK was found, confirming our diagnosis.

in Case 1 was previously reported in Indian patients with HIDS. Enzyme assays could have offered confirmatory evidence by demonstrating reduced mevalonate kinase activity. Urinary mevalonic acid quantification also serves as a useful biomarker[7].

The mainstay of HIDS treatment lies in managing acute febrile attacks using high-dose NSAIDs, steroids, and biological agents like anakinra or canakinumab. The long-term outlook is relatively better than other hereditary periodic fevers. In contrast, mevalonic aciduria has a poorer prognosis with no definitive cure available currently[8,9]. Supportive treatment modalities targeting organ damage, infections, nutrition, and developmental delays can help counter morbidity. Allogeneic hematopoietic stem cell transplantation may offer the only potential cure in rapidly progressive cases.

A review by Isabelle Touitou *et al*.highlighted that the modes of inheritance vary, being recessive for systemic subtypes and dominant with post-zygotic somatic genetic alterations for MVK-associated porokeratosis.[10]

Conclusion

These cases contribute to the limited literature on mevalonate kinase deficiency in the Indian population, highlighting the diverse clinical presentations and the importance of genetic confirmation for accurate diagnosis. The challenges in timely diagnosis, misdiagnoses, and limited therapeutic success underscore the need for increased awareness, early genetic testing, and comprehensive long-term care for individuals with MKD.

References

1. Zhang S. Natural history of mevalonate kinase deficiency: a literature review. Pediatr Rheumatol Online J 2016;14(1):30.
2. Favier LA, Schulert GS. Mevalonate kinase deficiency: current perspectives. Appl Clin Genet 2016 ;9:101–10.
3. Bader-Meunier B, Florkin B, Sibilia J, Acquaviva C, Hachulla E, Grateau G, et al. Mevalonate Kinase Deficiency: A Survey of 50 Patients. Pediatrics 2011 ;128(1):e152–9.
4. Govindaraj GM, Jain A, Peethambaran G, Bhoyar RC, Vellarikkal SK, Ganapati A, et al. The spectrum of clinical features and genetic variants in the mevalonate kinase (MVK) gene of South Indian families suffering from Hyperimmunoglobulin D Syndrome. PloS One 2020;15(8):e0237999.
5. ter Haar NM, Jeyaratnam J, Lachmann HJ, Simon A, Brogan PA, Doglio M, et al. The Phenotype and Genotype of Mevalonate Kinase Deficiency: A Series of 114 Cases From the Eurofever Registry. Arthritis Rheumatol 2016;68(11):2795–805.
6. Zhang SQ, Jiang T, Li M, Zhang X, Ren YQ, Wei SC, et al. Exome sequencing identifies MVK mutations in disseminated superficial actinic porokeratosis. Nat Genet 2012 ;44(10):1156–60.
7. Jeyaratnam J, Frenkel J. Management of Mevalonate Kinase Deficiency: A Pediatric Perspective. Front Immunol [Internet]. 2020 [cited 2023 Nov 28];11. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2020.01150
8. Evidence-based recommendations for the practical management of Familial Mediterranean Fever | Request PDF [Internet]. [cited 2023 Nov 28]. Available from: https://www.researchgate.net/publication/237069289_Evidence-based_recommendations_for_the_practical_management_of_Familial_Mediterranean_Fever
9. Management of Mevalonate Kinase Deficiency: A Pediatric Perspective - PMC [Internet]. [cited 2023 Nov 28]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7289972/
10. Touitou I. Twists and turns of the genetic story of mevalonate kinase-associated diseases: A review. Genes Dis 2022 ; 9(4):1000–7.