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MEVALONATE KINASE DEFICIENCY PRESENTING WITH RECURRENT GROSS HEMATURIA AND ACUTE KIDNEY INJURY: A RARE PAEDIATRIC CASE REPORT WITH THREE-YEAR FOLLOW-UP

Deepa Ganapathi* Department of Paediatrics, Grant Government Medical College and Sir J.J. Group of Hospitals, Mumbai, India *Corresponding Author

Bela Verma Department of Paediatrics, Grant Government Medical College and Sir J.J. Group of Hospitals, Mumbai, India

Kaif Charania Department of Paediatrics, Grant Government Medical College and Sir J.J. Group of Hospitals, Mumbai, India

ABSTRACT **Background:** Mevalonate kinase deficiency (MKD), clinically classified as Hyper immunoglobulin D Syndrome (HIDS), is an autosomal recessive autoinflammatory disorder arising from biallelic pathogenic variants in the MVK gene. Affected individuals experience stereotyped periodic febrile episodes, cervical adenopathy, polyarthralgia, and abdominal symptoms. Frank hematuria concurrent with acute kidney injury (AKI) represents an exceptionally rare and diagnostically demanding phenotypic variant. **Case Presentation:** A 9-year-old boy was admitted with episodic high-grade fever, recurrent macroscopic hematuria, and AKI of undetermined origin. Three years later, at age 12, he re- attended with a pan-articular inflammatory flare involving all four limbs, precipitated by an antecedent respiratory infection; renal indices had by then normalised. Whole exome sequencing (WES) identified a homozygous likely pathogenic variant in MVK [NM_000431.4: c.925G>A (p.Gly309Ser)], confirming the diagnosis. An incidentally discovered hemizygous pathogenic variant in G6PD [c.949G>A (p.Glu317Lys)] was additionally found. Colchicine and NSAIDs provided insufficient disease control; sustained remission was achieved only after IL- 1 receptor blockade with anakinra. **Conclusion:** This report broadens the recognised phenotypic spectrum of HIDS to encompass hematuria and AKI in a South Asian child. Genomic characterisation via WES is indispensable when clinical features are atypical, and timely IL-1 pathway inhibition delivers meaningful benefit in treatment-refractory disease.

KEYWORDS : HIDS; Mevalonate Kinase Deficiency; MVK Mutation; Periodic Fever; Hematuria; Acute Kidney Injury; Whole Exome Sequencing; Anakinra

INTRODUCTION

Mevalonate kinase deficiency (MKD), widely designated Hyper-immunoglobulin D Syndrome (HIDS), is a recessively inherited autoinflammatory condition caused by biallelic loss-of-function variants in the MVK gene, located on chromosome 12q24. [1,2] The gene product, mevalonate kinase (MK), phosphorylates mevalonic acid within the isoprenoid biosynthetic cascade. Enzyme insufficiency reduces downstream non-sterol isoprenoid output, producing dysregulated GTPase Rac1 signalling and sustained interleukin-1β (IL-1β) overproduction that perpetuates periodic systemic inflammation. [3] Globally, fewer than 300 genetically confirmed cases are on record, with a marked concentration in Northern European populations. [4]

The prototypical phenotype consists of self-limited febrile episodes of 3–7 days recurring every 3–6 weeks, typically accompanied by cervical adenopathy, abdominal pain, polyarthralgia, and erythematous cutaneous eruptions. [4] Nephrological involvement in the form of hematuria and AKI is seldom encountered and can closely simulate primary glomerulonephritis or alternative hereditary fever syndromes, most notably Familial Mediterranean Fever (FMF). [8] Herein we describe a molecularly confirmed paediatric HIDS case in whom recurrent frank hematuria and AKI were the dominant presenting features, compounded by an incidentally identified G6PD deficiency detected on WES, underscoring the indispensable role of comprehensive genomic sequencing in phenotypically atypical autoinflammatory disease.

Case Report

Initial Presentation (Age 9 Years, 2022)

Master S.S., a 9-year-old boy and the seventh child in his family, was brought to the Paediatrics Department of Grant Government Medical College and Sir J.J. Group of Hospitals, Mumbai, with a presenting triad of high-grade fever, cough, and macroscopic hematuria. His parents recalled at least three years of cyclically recurring identical episodes, each resolving spontaneously over 3–7 days. During the index admission, multiple superimposed attacks arose, each featuring fever, hematuria, and colicky abdominal pain. As the hospitalisation extended, bilateral elbow and knee arthritis with periarticular swelling became apparent.

Genealogical enquiry revealed a compelling family background: four prior siblings (the 1st, 3rd, and 4th-born males and the 5th-born female) had each died in infancy, attributed by the family to respiratory causes. This clustering of early sibling deaths raised strong suspicion for a recessively inherited autoinflammatory or primary immunodeficiency syndrome. The indexpatient himself had undergone exploratory laparotomy at one year of age for an uncharacterised abdominal condition, without a definitive surgical diagnosis being established.

Physical examination documented pallor and generalised wasting; the spleen was enlarged to a moderate degree. Peripheral lymphadenopathy and cutaneous rash were absent. Whole exome sequencing subsequently yielded the molecular diagnosis of HIDS (see Investigations). An initial regimen of colchicine, NSAIDs, and intermittent subcutaneous anakinra resulted in progressive resolution of hematuria and recovery of renal function.

Follow-up Presentation (Age 12 Years, 2026)

At age 12 — three years after his initial discharge — the patient re-presented with a four-week history of worsening bilateral upper and lower limb dysfunction: joint pain, periarticular swelling, and severely restricted range of motion. One week before joint symptoms appeared, he had experienced an upper respiratory tract infection (cough, nasal congestion, and pharyngitis) — a well-documented precipitant of HIDS flares. Clinical photographs taken during this admission (with written parental consent; Figure 2) showed a thin, undernourished habitus alongside bilateral elbow swelling and restricted wrist extension.

Examination confirmed persisting pallor and wasting; active synovitis with painful restriction of movement was evident across bilateral elbow, wrist, knee, and ankle joints. Moderate splenomegaly was again palpable. Specialist rheumatological assessment by Dr. Raju Khubchandani (SRCC Hospital, Mumbai) corroborated an active flare of this genetically established HIDS case. Ophthalmological evaluation was unremarkable. Urinalysis yielded no hematuria, consistent with sustained inflammatory control over the preceding three years.

Investigations

Serial hematological, biochemical, and molecular investigations conducted at both admissions are compared in Table 1; WES molecular findings are summarised in Table 2.

Table 1. Laboratory Investigations — Index Admission (Age 9, 2022) vs. Follow-up (Age 12, 2026)

Investigation	Index 2022 (Age 9)	Follow-up 2026 (Age 12)	Comment

Haemoglobin	6.2 g/dL	8.1 g/dL	Improved; anaemia persists
Total Leucocyte Count	39,000/cumm	17,110/mm³	Reduced; still elevated
Platelet Count	1.44×10^5/µL	315×10^3/mm³	Normal
Serum Creatinine	2.9 mg/dL	0.7 mg/dL	Normalised — AKI resolved
Blood Urea	44 mg/dL	Not repeated	
Total Bili/SGOT/SGPT	Not done	0.2/13/7 mg-IU/L	Normal
Urine RBC	>300/HPF	Not significant	Haematuria resolved
ESR	67 mm/hr	70 mm/hr	Persistently elevated
Serum Ferritin	889 ng/mL	Not repeated	Markedly elevated at index
Serum IgA	421 mg/dL	Not repeated	Elevated (ref <260)
ANA/ Complement C3	Neg/89.7 mg/dL	Not repeated	Low-normal C3
USG Abdomen	Hepato-splenomegaly; raised kidney echogenicity	Mild splenomegaly only	Renal changes resolved
Renal Biopsy	Normal histology	Not repeated	No nephritis at index
Ophthalmology	Not done	No abnormality	Eyes unaffected

AKI = Acute Kidney Injury; HPF = High Power Field; USG = Ultrasonography.

Whole Exome Sequencing

Whole exome sequencing disclosed a homozygous likely pathogenic missense variant in MVK [c.925G>A (p.Gly309Ser), Exon 10], concordant with a molecular diagnosis of HIDS/MKD (OMIM #260920). The allele is absent from gnomAD South Asian population databases, classified as deleterious by both SIFT and PolyPhen-2 in silico prediction tools, and was previously documented in the literature by Cuisset et al. [5] Variant pathogenicity was graded according to ACMG/AMP consensus criteria. [6] An incidentally identified hemizygous pathogenic variant in G6PD [c.949G>A (p.Glu317Lys), Exon 9] was concurrently found, mandating strict avoidance of haemolysis-triggering oxidative stressor agents. [7](Table 2).

Table 2. WES — Clinically Significant Variants

Gene	Variant (HGVS)	Location	Zygosity	Disorder (OMIM)	Classification
MVK	NM_000431.4: c.925G>A (p.Gly309Ser)	Exon 10	Homozygous	HIDS (#260920) / Mevalonic Aciduria (#610377)	Likely Pathogenic
G6PD	NM_001042351.3: c.949G>A (p.Glu317Lys)	Exon 9	Hemizygous	G6PD Deficiency (#300908)	Pathogenic (incidental)

HIDS = Hyperimmunoglobulinemia D Syndrome; OMIM = Online Mendelian Inheritance in Man.

Treatment

Initial Regimen (2022)

Pharmacological management was escalated in a stepwise fashion. Colchicine (0.03 mg/kg/day) was introduced as the first-line agent. Naproxen (10 mg/kg/dose twice daily) was co-prescribed for symptomatic relief during febrile attacks. Prednisolone (2 mg/kg/day for 3 days) was incorporated when arthritis proved unresponsive to NSAIDs alone. Owing to a persistently inadequate overall response, subcutaneous anakinra — an IL-1 receptor antagonist (1 mg/kg/day for 5 days) — was administered on an intermittent, attack-triggered schedule; this yielded a clinically perceptible reduction in both the severity and the duration of inflammatory episodes. [10] Hematuria abated and renal function recovered progressively as disease activity was brought under control. The child was thereafter maintained on intermittent anakinra, with serial monitoring of renal indices and injection-site reactions.

Revised Regimen at 2026 Follow-up

Specialist rheumatological review at the 2026 re-admission by Dr. Raju Khubchandani (SRCC Hospital, Mumbai) confirmed an active flare in this genetically established HIDS case. While anakinra represents the preferred agent for refractory MKD, its absence from the public-sector formulary and the prohibitive out-of-pocket cost precluded continued use. [11] A resource- adapted regimen was accordingly formulated: (1) uninterrupted daily colchicine irrespective of symptom status; (2) naproxen reserved for active flares; (3) short-course prednisolone 1 mg/kg/day for 3–5 days during severe exacerbations; (4) supplementation with iron, calcium, and vitamin E to address the child's chronic anaemia and nutritional deficits. A three-month follow-up appointment was arranged.

DISCUSSION

Among the hereditary periodic fever syndromes, HIDS is exceptionally uncommon; a South Asian paediatric presentation dominated by hematuria and AKI is particularly outside the classical phenotypic description. [2,4] The principal diagnostic challenge was excluding conditions with overlapping features: FMF, IgA nephropathy, TRAPS, and cyclic neutropenia were each systematically considered. Non-detection of MEFV pathogenic variants on WES, combined with the stereotyped febrile attack pattern and the homozygous MVK c.925G>A allele, established the diagnosis of HIDS. [14]

The standard clinical criteria for HIDS comprise fever surpassing 38.5°C for 3–7 days, cervical adenopathy, abdominal distress, arthralgia, and raised serum IgD (>100 IU/mL) with concurrent IgA elevation. [4] In this patient, serum IgA was markedly elevated at 421 mg/dL. IgD was not measured at initial presentation — a recognised limitation in clinical practice — though this biomarker may lie within the normal range in young children and its absence does not preclude the diagnosis when molecular confirmation is obtained. [5]

Renal manifestations of MKD remain sparsely reported in the literature. Hematuria in this context most likely reflects inflammation-mediated glomerular or tubulo-interstitial microangiopathy occurring at the peak of febrile episodes. [8] A histologically normal renal biopsy, as in this case, does not exclude functionally driven hematuria, since pathological changes may be transient or sub-threshold on light microscopy. Reversible AKI in MKD has been attributed to dehydration, intravascular hemolysis, or a direct nephritogenic effect of the inflammatory cascade. Clinicians must be alert to this unusual phenotype to forestall misclassification as primary glomerulonephritis.

The family pedigree merits careful consideration. Four siblings dying within the first year of life represent a significant early-childhood mortality burden within a single kindred, with respiratory illness cited as the attributed cause. Complete MK deficiency (mevalonic aciduria) produces a phenotype far more severe than HIDS: affected infants may develop failure to thrive, psychomotor regression, multi-organ crises, and death within infancy. [9]The clinical profile of the deceased siblings makes undiagnosed mevalonic aciduria a plausible retrospective diagnosis. Cascade WES of surviving family members and appropriate genetic counselling are therefore strongly indicated. [6]

The incidentally identified hemizygous G6PD variant (p.Glu317Lys) carries concrete pharmacological consequences. Oxidant-class drugs — including primaquine, dapsone, nitrofurantoin, and cotrimoxazole — together with dietary fava bean consumption, must be categorically prohibited to prevent acute hemolytic crisis, a concern particularly germane given this child's baseline chronic anemia. [7]

From a therapeutic perspective, colchicine provides limited benefit in MKD compared to its established efficacy in FMF. NSAIDs afford partial symptomatic relief without altering the underlying disease trajectory, and corticosteroids deliver only transient and incomplete suppression. The strongest evidence for disease modification rests with IL-1 pathway blockade: intermittent anakinra yielded measurable reductions in attack frequency and severity in this patient, consistent with published trial data. [10] For those with frequent relapse or suboptimal anakinra responses, the long-acting IL-1β-targeted monoclonal antibody canakinumab constitutes a well-documented therapeutic alternative. [11,12] This case additionally confirms that WES not only resolves diagnostic uncertainty in phenotypically atypical periodic fever but simultaneously uncovers co-morbid genetic findings with direct clinical relevance.

Three instructive insights arise from the 2026 follow-up visit. First, complete disappearance of hematuria and near-normalisation of serum creatinine (2.9 → 0.7 mg/dL) over three years of sustained inflammatory control demonstrates that MKD-related renal injury is potentially reversible — a meaningful prognostic reassurance for long-term counselling. [8] Second, pan- articular involvement affecting all four limbs at age 12, in a child whose earlier arthritis was more restricted, illustrates that the musculoskeletal phenotype of HIDS is not static and may broaden progressively through adolescence. [4] Third, the financial inaccessibility of biologics within India's public health infrastructure necessitated pragmatic de-escalation to a continuous colchicine-based strategy — an operational challenge seldom reflected in Western treatment algorithms. Daily maintenance colchicine, rather than purely symptom-triggered use, may confer incremental anti-inflammatory benefit consistent with approaches employed in related autoinflammatory conditions. [11]

Key Learning Points

- HIDS warrants consideration in children with unexplained periodic fever and hematuria or AKI, irrespective of ethnic background.
- A histologically normal renal biopsy does not exclude HIDS-associated nephrological injury, which may be functionally driven and transient.
- WES is the diagnostic cornerstone for atypical or treatment-refractory hereditary periodic fever syndromes.
- Homozygous MVK c.925G>A (p.Gly309Ser) in a South Asian child broadens the geographic and ethnic phenotypic spectrum of HIDS.
- Incidental G6PD deficiency identified on WES has immediate pharmacological consequences requiring clinical action.
- Intermittent anakinra achieves meaningful control in colchicine/ NSAID-refractory HIDS; canakinumab is an evidence-based option for frequently relapsing disease.
- MKD-associated renal involvement is reversible: sustained creatinine normalisation over three years confirms the prognostic value of maintained inflammatory control.
- The articular phenotype of HIDS may widen with age; pan-articular disease can emerge in adolescence even in patients with previously limited joint involvement.
- Where biologic therapy is inaccessible, continuous daily colchicine combined with on- demand NSAIDs and short-course corticosteroids is clinically rational and guideline- consistent.

Figures

Figure 1 · Pedigree

Family Pedigree — HIDS (Hyperimmunoglobulin D Syndrome) Three-generation Pedigree; Index Case Master S.S. (7th born, 9 Years, Proband)

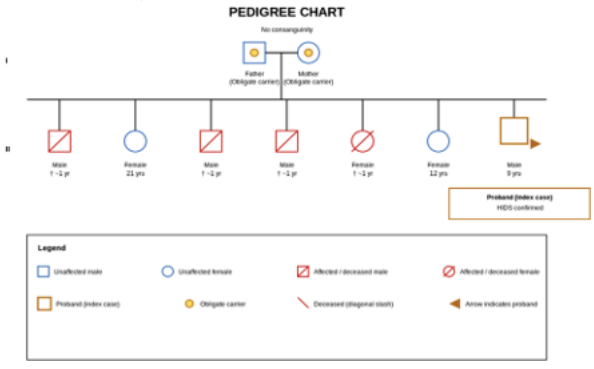

Figure 1. Three-generation family pedigree of the index case (Master S.S., 7th born, 9 years). Generation I: parents (father and mother, non-consanguineous, obligate carriers of autosomal recessive MVK mutation). Generation II: seven siblings in birth order. Children 1, 3, 4 (males) and 5 (female) died at approximately one year of age due to reported respiratory causes; possible undiagnosed mevalonic aciduria (complete MK deficiency) cannot be excluded in these siblings. Child 2 (female, 21 years) and Child 6 (female, 12 years) are phenotypically unaffected. Child 7 (male, 9 years) is the proband — confirmed HIDS with homozygous MVK c.925G>A (p.Gly309Ser) mutation on whole exome sequencing. No consanguinity between parents. Carrier status of living siblings has not yet been determined; cascade genetic testing is recommended. Abbreviations: HIDS, hyperimmunoglobulin D syndrome; MK, mevalonate kinase; †, deceased.

Figure 2: Clinical Photographs at 2026 Admission (Parental Consent Obtained) — Wasted Habitus, Bilateral Elbow Swelling, Restricted Wrist Movements.

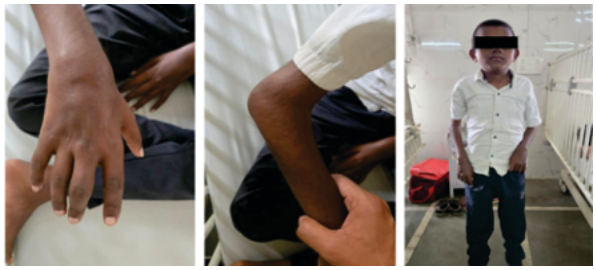

Figure 3: Diagnostic Criteria – Mevalonate Kinase Deficiency (MKD) / Hyper-IgD Syndrome (HIDS)

Section	Criteria
A. Clinical Criteria	• Recurrent fever starting in early infancy (<1 year) • Fever episodes lasting 3–7 days • Recurrence every 4–8 weeks • Fever associated with ≥3 of the following: – Cervical lymphadenopathy – Abdominal pain / vomiting / diarrhea – Arthralgia or arthritis – Skin lesions (maculopapular rash / purpura) • Episodes triggered by vaccination, minor trauma, or stress
B. Laboratory Criteria	• Elevated serum IgD (>100 U/mL) on two occasions (≥1 month apart) • Elevated serum IgA • Increased urinary mevalonic acid during attacks • Elevated CRP and Serum Amyloid A during episodes
C. Diagnostic Confirmation	• Mutation in the MVK (mevalonate kinase) gene on genetic testing

Figure 4 · Clinical Course

Disease Progression & Treatment Escalation in HIDS (2022–2026) Fever/Haematuria Episode Pattern and Treatment Escalation Across 4-year Follow-up (Index 2022 to Polyarticular Flare 2026)

Figure 4. Clinical timeline of disease course in Master S.S. (confirmed HIDS; MVK c.925G>A homozygous). Index presentation age 9 (2022) through follow-up re-admission age 12 (2026). Symptom rows depict fever episodes (3– 7 days, 3–6 week intervals), concurrent gross haematuria, episodic abdominal pain, and joint involvement from~Month 3. Episode bars decrease in size and opacity after Month 6, reflecting reduced attack severity. Treatment escalation: colchicine at M0 (continued throughout); NSAIDs (naproxen) PRN during attacks M0–M4; three 3-day prednisolone pulses for arthritis at M3, M4, M5; subcutaneous anakinra commenced at M6 (pink dot, dashed pivot line) after inadequate response to prior therapies. Abbreviations: HIDS, hyperimmunoglobulinemia D syndrome; AKI, acute kidney injury; PRN, as needed; IL-1, interleukin-1; SC, subcutaneous; M, month from first presentation.

CONCLUSION

A genetically confirmed HIDS diagnosis in a South Asian boy — presenting with recurrent hematuria and AKI at age 9 and subsequently developing pan-articular disease at age 12 — materially expands the known phenotypic boundaries of mevalonate kinase deficiency. Longitudinal observation over three years documented complete reversal of renal injury under maintained inflammatory control, providing an important prognostic benchmark. Molecular diagnosis through WES was indispensable, simultaneously disclosing the causative homozygous MVK variant and a clinically actionable incidental G6PD finding. The real-world inaccessibility of biologic therapy in resource-constrained healthcare settings underscores the urgent need for feasible, locally adaptable therapeutic algorithms. Cascade genetic evaluation of surviving family members alongside pre-conception counselling remains strongly recommended.

Declarations

Patient Consent: Written informed consent was obtained from the parents for publication of this case report.

Conflicts of Interest: None declared. Funding: None.

Ethical Approval: Not applicable (case report).

Author Contributions: DG: primary clinician, case management, manuscript drafting, conference presentation, data collection; BV: conceptualisation, supervision, critical revision, follow-up management,; KC: investigations, literature review, manuscript review;.

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