Case Report

Early genetic diagnosis of thymidine kinase 2-related mitochondrial DNA depletion syndrome in a neonate with respiratory failure: A rare case highlighting the role of early genetic diagnosis and ethical decision-making

Mukesh Kumar[1], Tauhid Iqbali[2], Harpreet Singh[3], Ravi Shah[1]

From [1]Doctor of Medicine, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, [2]Doctor of Medicine, Department of Pediatrics, Patna Medical College, Patna, Bihar, [3]Doctor of Medicine, Department of Pediatrics, Government Medical College, Jammu, Jammu and Kashmir, India

ABSTRACT

Mitochondrial DNA (mtDNA) depletion syndromes represent a heterogeneous group of autosomal recessive disorders characterized by a significant reduction in mtDNA copy number, leading to impaired oxidative phosphorylation and severe multisystem disease. The myopathic form caused by mutations in the thymidine kinase 2 (*TK2*) gene is particularly rare and often presents in infancy with profound muscle weakness and respiratory failure. We report a rare case of infantile-onset TK2-related mtDNA depletion syndrome presenting in the immediate neonatal period with severe hypotonia and respiratory failure. Early genetic diagnosis enabled appropriate counseling and facilitated informed decision-making by the family. This case underscores the importance of considering mitochondrial disorders in neonates with unexplained hypotonia and respiratory insufficiency.

Key words: Genetic counseling, Mitochondrial DNA depletion syndrome, Neonatal hypotonia, Rare genetic disease, Respiratory failure in neonate, *TK2* gene mutation

Mitochondrial DNA depletion syndromes (MDDSs) are a group of inherited disorders characterized by a marked reduction in mitochondrial DNA (mtDNA) copy number within affected tissues, leading to impaired oxidative phosphorylation and cellular energy failure. These disorders typically present in infancy or early childhood and can involve skeletal muscle, liver, brain, or multiple organ systems [1,2]. Mutations in the thymidine kinase 2 (*TK2*) gene are responsible for the myopathic form of MDDS, which primarily affects skeletal muscle and respiratory musculature. TK2 is a mitochondrial enzyme involved in the phosphorylation of deoxythymidine and deoxycytidine, a critical step in the mitochondrial nucleotide salvage pathway required for mtDNA replication and maintenance [3]. The prevalence of TK2-related MDDS is extremely low, with infantile-onset cases representing the most severe phenotype. These patients typically present with profound hypotonia, feeding difficulties, respiratory failure, and progressive muscle weakness [4].

Access this article online	
Received - 06 March 2026 Initial Review - 18 March 2026 Accepted - 06 April 2026	Quick Response code
DOI: ***	

We present a rare neonatal case of TK2-associated MDDS, highlighting the clinical features, diagnostic approach, and the importance of early genetic confirmation for appropriate counseling and management.

CASE PRESENTATION

A 25-year-old primigravida with an otherwise uneventful antenatal course was referred for further evaluation at 32 weeks and 4 days of gestation. Earlier, the first-trimester aneuploidy screening and anomaly scan were reported as normal. However, a third-trimester ultrasound performed for fetal growth assessment demonstrated intrauterine growth restriction with mild polyhydramnios, along with non-visualization of the fetal stomach and scalp edema, raising suspicion of esophageal atresia.

Subsequently, the patient underwent emergency lower-segment cesarean section in view of non-reassuring fetal heart rate. A female neonate was delivered. During delivery, the fetal body appeared unusually rigid. APGAR scores were 3 and 5 at 1 and 5 min of life. The infant cried poorly immediately after birth but soon developed poor respiratory effort on day 1 of life and

Correspondence to: Dr. Mukesh Kumar, Department of Obstetrics and Gynaecology, AIIMS Rishikesh, Punjab, India. E-mail: dr.mukeshkr1994@gmail.com

generalized hypotonia. On initial clinical examination, the neonate was non-vigorous, hypotonic, and limp, with limb contractures and reduced spontaneous movements. The infant developed Type II respiratory failure shortly after birth, necessitating mechanical ventilatory support and admission to the neonatal intensive care unit.

Given the antenatal findings of polyhydramnios and an absent fetal gastric bubble, tracheoesophageal fistula was initially suspected. Despite intensive neonatal care, the neonate continued to demonstrate severe generalized hypotonia, persistent respiratory insufficiency, and evidence of early muscle involvement, raising suspicion of an underlying neuromuscular or metabolic disorder.

Genetic testing using whole exome sequencing identified a pathogenic homozygous mutation in the *TK2* gene, confirming the diagnosis of MDDS type 2 (OMIM#609560), an autosomal recessive disorder.

Infantile-onset TK2 deficiency is associated with a severe and rapidly progressive clinical course, frequently resulting in early respiratory failure and high mortality during infancy. Given the early onset of symptoms, severity of disease, irreversible respiratory muscle involvement, and extremely poor prognosis, extensive counseling was provided to the parents regarding the nature of the disorder, expected disease trajectory, and quality-of-life considerations. After multidisciplinary discussions involving the neonatology and genetics teams, the parents made an informed decision to refer the neonate to a higher center for advanced management.

DISCUSSION

MDDSs represent an important but rare group of disorders that should be considered in neonates presenting with unexplained hypotonia, respiratory insufficiency, and muscle weakness. Mutations in the *TK2* gene impair mitochondrial nucleotide salvage pathways required for mtDNA replication, leading to severe depletion of mtDNA in muscle tissue and resulting in profound myopathy.

Clinical manifestations of infantile-onset TK2 deficiency include severe hypotonia at birth, feeding difficulties, respiratory insufficiency, progressive muscle weakness, and early respiratory failure [2]. Martín-Hernández *et al*. described a case of TK2-related myopathic MDDS presenting with proximal muscle weakness, elevated creatine kinase, and isolated complex III deficiency. Genetic analysis revealed a homozygous (*TK2;* NM_004614.4:c.323 C>T, p.T108M) mutation with severe mtDNA depletion (<20%), yet the clinical course was relatively mild and slowly progressive, highlighting significant phenotypic variability in TK2 deficiency [1]. Another case reported by Murata *et al*., a 2-year-old male, first child of non-consanguineous parents, presented at 17 months with regression of previously attained age-appropriate motor milestones since 12 months. Examination revealed generalized hypotonia, hyporeflexia, and reduced voluntary movements, with no other abnormalities. Genetic testing confirmed MDDS type 2. The patient was managed with gastrostomy, tracheostomy, and multidisciplinary care [5].

Recent advances have suggested the potential role of nucleoside replacement therapy in certain patients with TK2 deficiency, although outcomes remain variable and early diagnosis remains critical [6]. Early identification of mitochondrial disorders through genetic testing plays a crucial role in avoiding prolonged futile interventions, facilitating accurate diagnosis, enabling informed parental decision-making, and providing appropriate genetic counseling for future pregnancies.

Genetic counseling is an essential aspect of care in families affected by TK2-related MDDS. As the disorder follows an autosomal recessive inheritance pattern, both parents are typically asymptomatic carriers, and the recurrence risk in subsequent pregnancies is 25%. Identification of the pathogenic mutation allows targeted carrier testing and enables prenatal diagnosis through chorionic villus sampling or amniocentesis in future pregnancies [7]. Prenatal genetic testing is possible if the mutation is known, and preimplantation genetic testing can be offered to prevent recurrence. Early genetic diagnosis, therefore, plays a crucial role not only in clinical management but also in providing families with accurate information regarding recurrence risk and reproductive options [8].

CONCLUSION

This case highlights the importance of considering mitochondrial disorders in neonates presenting with severe hypotonia and respiratory failure of unclear etiology. Early genetic diagnosis enables accurate disease identification and plays a vital role in guiding clinical management, ethical decision-making, and reproductive counseling. Timely diagnosis allowed the family to make informed decisions and provided critical information for future pregnancy planning.

REFERENCES

1. Martín-Hernández E, García-Silva MT, Quijada-Fraile P, Rodríguez-García ME, Rivera H, Hernández-Laín A, *et al*. Myopathic mtDNA depletion syndrome due to mutation in *TK2* Gene. Pediatr Dev Pathol 2017;20:416-20.
2. Nogueira C, Almeida LS, Nesti C, Pezzini I, Videira A, Vilarinho L, *et al*. Syndromes associated with mitochondrial DNA depletion. Ital J Pediatr 2014;40:34.
3. Domínguez-González C, Madruga-Garrido M, Mavillard F, Garone C, Aguirre-Rodríguez FJ, Donati MA, *et al*. Deoxynucleoside therapy for thymidine kinase 2-deficient myopathy. Ann Neurol 2019;86:293-303.
4. Basel D. Mitochondrial DNA depletion syndromes. Clin Perinatol 2020;47:123-41.
5. Murata AS, Avelino GH, Algazal MM, Utino EA, Gonçalves CS, Ribeiro AA. Case report: Mitochondrial DNA depletion syndrome 2. Arq Neuropsiquiatr 2024;82: S53-176.

6. El-Hattab AW, Scaglia F. Mitochondrial DNA depletion syndromes: Review and updates of genetic basis, manifestations, and therapeutic options. Neurother J Am Soc Exp Neurother 2013;10:186-98.
7. Parikh S, Goldstein A, Koenig MK, Scaglia F, Enns GM, Saneto R, *et al*. Diagnosis and management of mitochondrial disease: A consensus statement from the mitochondrial medicine society. Genet Med 2015;17:689-701.
8. Gorman GS, Chinnery PF, DiMauro S, Hirano M, Koga Y, McFarland R, *et al*. Mitochondrial diseases. Nat Rev Dis Primer 2016;2:16080.

Funding: Nil; Conflicts of interest: Nil.

How to cite this article: Kumar M, Iqbali T, Singh H, Shah R. Early genetic diagnosis of thymidine kinase 2-related mitochondrial DNA depletion syndrome in a neonate with respiratory failure: A rare case highlighting the role of early genetic diagnosis and ethical decision-making. Indian J Case Reports. 2026; April 12 [Epub ahead of print].