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Case Report

King-Denborough syndrome: a clinicogenetic case report

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ABSTRACT

King–Denborough syndrome is a rare RYR1-related congenital myopathy characterized by dysmorphic features, muscle weakness, and susceptibility to malignant hyperthermia, often posing a diagnostic challenge in early infancy. We report a one-year-old female child presenting with developmental delay and generalized hypotonia. Clinical evaluation revealed craniofacial dysmorphism, bilateral ptosis, and esotropia, raising suspicion of an underlying congenital myopathy. Initial laboratory and imaging workup were inconclusive except for transient elevation of creatine kinase. Whole exome sequencing identified a heterozygous missense variant in the RYR1 gene (c.14126C>T; p.Thr4709Met), along with a likely pathogenic FOXP1 variant. In view of the characteristic clinical phenotype, a diagnosis of King–Denborough syndrome was considered. The child was managed with supportive therapy and developmental interventions, and caregivers were counselled regarding the risk of malignant hyperthermia. This case underscores the importance of clinicogenetic correlation in diagnosing rare myopathies and highlights the need for early recognition to enable appropriate counselling and prevention of anaesthetic complications.

Keywords: King–Denborough syndrome, RYR1 gene, Congenital myopathy, Hypotonia, Malignant hyperthermia, Developmental delay

INTRODUCTION

Congenital myopathies constitute a group of inherited neuromuscular disorders that commonly present during infancy or early childhood. These conditions are characterized by decreased muscle tone, muscle weakness, and delayed acquisition of motor milestones.[1] King–Denborough syndrome (KDS) is a rare autosomal dominant congenital myopathy caused by mutations in the RYR1 gene, characterized by a triad of dysmorphic features, muscle weakness, and susceptibility to malignant hyperthermia.[2]

Advances in molecular diagnostic techniques have significantly improved the ability to identify the genetic basis of many congenital myopathies. Several genes involved in skeletal muscle excitation–contraction coupling, structural integrity, and intracellular calcium regulation have been implicated.[3] Among these, the RYR1 gene is one of the most frequently involved. RYR1 encodes the skeletal muscle ryanodine receptor, which regulates intracellular calcium release required for normal skeletal muscle contraction. This receptor plays an essential role in excitation–contraction coupling by regulating the release of calcium ions necessary for muscle contraction.[4] Variants in the RYR1 gene have been associated with a spectrum of clinical conditions, including central core disease, multiminicore disease, congenital myopathy, King–Denborough syndrome, and susceptibility to malignant hyperthermia.[3-5] King–Denborough syndrome occupies a unique position within this spectrum due to its association with craniofacial dysmorphism, ophthalmologic abnormalities, and anaesthetic risk. We describe an infant presenting with developmental delay, generalized hypotonia, craniofacial dysmorphism, and ocular abnormalities, in whom a

heterozygous RYR1 variant was identified, consistent with King–Denborough syndrome. This case illustrates the importance of correlating genetic findings with clinical features when evaluating suspected congenital myopathies.

CASE REPORT

A one-year-old female child was brought for evaluation of delayed developmental milestones and generalized hypotonia. She was the first child born to non-consanguineous parents. There was no significant family history of neuromuscular disorders or developmental delay.

She was born at 36 weeks of gestation by normal vaginal delivery with a birth weight of 2.8 kg. The antenatal period was uneventful. There was no history of perinatal asphyxia, neonatal seizures, or requirement of prolonged neonatal intensive care. The parents reported delayed attainment of developmental milestones, particularly in the motor domain. At the time of evaluation, head control was delayed, sitting was partially achieved (grade I). Gross motor developmental age corresponded to approximately 6 months.

Figure 1: Phenotypic presentation of a case of King–Denborough syndrome.

On examination, the child was hypoactive and clumsy. Anthropometric parameters were within normal limits for age. Neurological examination revealed generalized hypotonia with preserved deep tendon reflexes. Craniofacial examination revealed fronto-parietal bossing.

Ocular examination demonstrated bilateral ptosis and bilateral esotropia and planned for squint surgery. The child was able to fix and follow objects horizontally, indicating preserved visual attention. No focal neurological deficits, or abnormal movements were observed. Cardiovascular and respiratory system examinations were normal. Considering a neuromuscular pathology, laboratory investigations were carried out and serum creatine kinase levels were elevated initially and showed a subsequent decline on repeat testing. Creatine kinase–MB levels were also mildly elevated. Thyroid function test, vitamin B12 levels, serum ferritin, and hemoglobin were within normal limits. Neurosonography and Echocardiography was performed which ruled out any structural abnormalities.

Genetic evaluation

Because of persistent hypotonia and developmental delay without a clear etiology on initial investigations, a genetic cause was suspected. The child underwent whole exome sequencing along with mitochondrial genome sequencing.

Genetic analysis identified a heterozygous missense variant in exon 96 of the RYR1 gene (c.14126C>T), resulting in substitution of methionine for threonine at amino acid position 4709 (p.Thr4709Met). The RYR1 gene has been associated with several neuromuscular conditions including congenital myopathy, King–Denborough syndrome, and susceptibility to malignant hyperthermia.[3-5] Although it remains classified as a Variant of uncertain significance (VUS) due to limited functional and segregation data, the clinical phenotype in this patient strongly supports its pathogenic relevance.

Table 1: Genetic study revealing RYR1 gene variant (C.14126C>T; P.THR4709MET), heterozygous VUS.

Gene# (transcrpit)	Location	Variant	Zygosity	DISEASE (OMIM)	Inheritance	Classification
RYR1 (+) (ENST00000359596.8) NM_000540.3	Exon 96	c.14126C>T (p. thr4709met)	Heterozygous**	Congenital myopathy 1a, with susceptibility to malignant hyperthermia (OMIM#117000) CONGENITAL myopathy 1b, autosomal recessive	Autosomal Dominant Autosomal Recessive**	Uncertain significance (PP1_SUP, PP3_SUP)

Continued.

Gene# (transcrpit)	Location	Variant	Zygosity	DISEASE (OMIM)	Inheritance	Classification
				(OMIM#255320) king-denborough syndrome (OMIM#619542)		

Note: _VS – Very Strong, _S – Strong, _M – Moderate, _Sup – Supporting.

Table 2: Genetic study revealing FOXP1 gene variant (C.886DUP; P.HIS296PROFSTER4), likely pathogenic.

Gene, variant details	Zygosity Depth (Alt allele %)	In silico tools	MAF	Literature	OMIM Disease	Inheritance	Classification
FOXP1 (-) **c.886dup** **p.His296ProfsTer4** **ENST00000649528.3** **NM_001349340.3**	Heterozygous 223X(49.3%)	SIFT - NA LRT - NA PolyPhen - NA PROVEAN - NA Meta SVM - NA FATHMM - NA ConDel - NA Splice AI -0	1000 G - NA gnomAD (V2.1) - NA gnomAD (V3.1) - NA MedVar - NA	-	Intellectual developmental disorder with language impairment with or without Autistic features (OMIM#613670)	Autosomal Dominant	Likely Pathogenic (PM2_M, PVS1_VS)

Note: VS - Very Strong, _S - Strong, _M - Moderate, _Sup – Supporting, D: Damaging; PrD: Probably Damaging; BN: Benign; T: Tolerated; MAF: Minor Allele Frequency; MedVar.

An additional heterozygous frameshift variant in the FOXP1 gene was also detected and classified as likely pathogenic. Variants in this gene are associated with intellectual developmental disorder and language impairment.[6]

However, at present the child has not yet demonstrated the full clinical phenotype typically associated with FOXP1-related disorders. Continued developmental monitoring is therefore warranted.

Management and follow-up

The child was managed conservatively with supportive therapy and developmental interventions. Parents were counselled regarding the potential risk of anaesthesia-related complications, particularly malignant hyperthermia, which has been associated with RYR1 gene variants.[7] They were advised to inform healthcare providers about this genetic finding before any surgical procedures requiring anaesthesia. Genetic counselling was provided, and the parents were advised to consider fetal medicine consultation before future pregnancies. The child was advised regular follow-up with developmental assessment and multidisciplinary care, including physiotherapy and supportive therapy aimed at improving motor development. The child continues to receive physiotherapy and developmental therapy, with regular follow-up for monitoring developmental progress.

DISCUSSION

King–Denborough syndrome is a rare but clinically important condition within the spectrum of RYR1-related myopathies characterized by a combination of congenital myopathy, dysmorphic facies, and susceptibility to malignant hyperthermia.[2] The present case demonstrates many of the classical features of the syndrome, including bilateral ptosis, esotropia, facial dysmorphism, generalized hypotonia, and delayed motor development.

Several studies have highlighted the variability in clinical presentation and genetic findings associated with this syndrome. A case series by Dowling et al evaluated four unrelated patients with KDS and demonstrated a relatively consistent clinical phenotype characterized by hypotonia, dysmorphic facies, and susceptibility to malignant hyperthermia. Importantly, heterozygous RYR1 mutations were identified in three of the four families, while one patient did not have an identifiable mutation, suggesting genetic heterogeneity in KDS.[8] The study also highlighted reduced RyR1 protein expression in affected individuals, supporting the role of impaired calcium homeostasis in disease pathogenesis. These findings are particularly relevant to the present case, where a heterozygous RYR1 variant of uncertain significance was identified, reinforcing the concept that even single variants may contribute to phenotype. Therefore, KDS should be considered a clinicogenetic diagnosis, where characteristic clinical features can

support the diagnosis even in the absence of definitive pathogenic variants.

An important clinical consideration in King–Denborough syndrome is that the condition may remain undiagnosed until an episode of malignant hyperthermia occurs during anaesthesia. Joseph et al described a pediatric case in which a child with pre-existing hypotonia and subtle dysmorphic features developed a hypermetabolic crisis intraoperatively, which subsequently led to the diagnosis of King–Denborough syndrome.[9] The child had clinical features comparable to those observed in our patient, including generalized hypotonia and craniofacial abnormalities, but these findings had not previously prompted a definitive diagnosis. It was only after the anaesthetic complication that further evaluation, including genetic testing, confirmed an underlying RYR1-related disorder. This highlights that children with mild or nonspecific neuromuscular signs may go unrecognized until exposed to triggering agents. Therefore, early identification and appropriate counselling are essential to prevent life-threatening complications during surgical procedures.

This case also highlights the role of early intervention. Although developmental delay persisted, the child showed gradual improvement in motor milestones with consistent physiotherapy and developmental therapy This aligns with existing literature suggesting that early rehabilitation can enhance functional outcomes in children with congenital myopathies, even in the presence of an underlying genetic etiology.[10]

Management of King–Denborough syndrome is primarily focused on supportive and rehabilitative measures aimed at maximizing functional ability and preventing complications. A multidisciplinary approach involving pediatricians, neurologists, physiotherapists, and developmental specialists is essential to optimize outcomes. Regular follow-up is required to monitor developmental progress, assess for emerging complications, and adjust therapeutic strategies accordingly. Particular attention must be paid to perioperative planning, as the risk of malignant hyperthermia necessitates avoidance of triggering anesthetic agents and the availability of dantrolene in emergency settings.[7,11]

Genetic counselling is a critical component of care in such cases. Families should be informed about the potential implications of RYR1 variants, including the risk of malignant hyperthermia and the possibility of variable expression among affected individuals. In view of the planned squint surgery, early identification of this syndrome is crucial to guide anaesthetic precautions and prevent malignant hyperthermia. Although the variant identified in this case is classified as a variant of uncertain significance, the strong clinicogenetic correlation warrants cautious interpretation and appropriate counselling. Discussion should include recurrence risk, the potential value of parental testing, and options for prenatal genetic diagnosis in future pregnancies.[3]

CONCLUSION

The present report highlights the need to consider King–Denborough syndrome among the differential diagnoses of infants presenting with developmental delay, generalized hypotonia, and dysmorphic craniofacial features. Identification of a heterozygous RYR1 variant, even when classified as a variant of uncertain significance, should prompt careful clinical evaluation and counselling regarding malignant hyperthermia risk. Early diagnosis enables appropriate management, anticipatory guidance, and prevention of potentially life-threatening complications.

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