CASO CLÍNICO/CASE REPORT

King-Denborough Syndrome: Report of a Family

Síndrome de King-Denborough: Relato de uma Família

João Vasco [1,*], Eulália Viveiros [1], Paula Pires [2]

1-Serviço de Pediatria / Hospital do Divino Espírito Santo de Ponta Delgada, EPER, Ponta Delgada, Açores, Portugal
2-Unidade de Neuropediatria do Serviço de Neurologia / Hospital de Santo Espírito da Ilha Terceira, EPER, Terceira, Açores, Portugal

DOI: https://doi.org/10.46531/sinapse/CC/230040/2023

Abstract

We report a case of an Azorean family with the diagnosis of the King-Denborough syndrome. Both mother and the two siblings present all the characteristic clinical findings of this syndrome – facial dysmorphias (with palpebral ptosis, malar hypoplasia, arched palate and micrognathia), musculoskeletal abnormalities (bell-shaped chest, pectus excavatum and lumbar hyperlordosis), diminished lower limbs strength with associated hyporeflexia and susceptibility to malignant hyperthermia. The diagnosis was possible after the youngest member of the family, now a 4-year-old girl, was born and referred to in-hospital consultation, due to the described constellation of dysmorphias and delay in motor development.

The aim of this article is to raise awareness to the importance of the correct investigation approach of a congenital myopathy, and in this specific case, to the importance of an early diagnosis that can be crucial to prevent a mostly fatal outcome for these patients.

Resumo

Neste artigo, reportamos o caso de uma família açoriana, com o diagnóstico de síndrome de King-Denborough. A mãe e os dois irmãos apresentam o fácies característico (com ptose palpebral bilateral, hipoplasia malar, palato em ogiva e micrognatia), as alterações músculo-esqueléticas (com tórax em sino, pectus excavatum e hiperlordose lombar), a diminuição da força muscular dos membros inferiores, hiporreflexia e uma suscetibilidade para hipertermia maligna – tudo parte do quadro clínico apresentado nesta síndrome. Nesta família o diagnóstico foi possível após estudo etiológico do membro mais novo, uma menina de 4 anos, referenciada à consulta de Pediatria pelas malformações já descritas e um atraso no desenvolvimento motor.

Pretendemos com este trabalho, sensibilizar para a importante marcha diagnóstica de uma miopatia congénita e, neste caso em específico, para o diagnóstico precoce como crucial para a prevenção de um desfecho na maioria das vezes fatal para estes doentes.

Informações/Informations:
Caso Clínico, publicado em Sinapse, Volume 23, Número 3, julho-setembro 2023. Versão eletrónica em www.sinapse.pt;
Case Report, published in Sinapse, Volume 23, Number 3, July-September 2023. Electronic version in www.sinapse.pt

Keywords:
Abnormalities, Multiple/diagnosis;
Malignant Hyperthermia;
Neuromuscular Diseases/diagnosis;
Ryanodine Receptor Calcium Release Channel/genetics;
Syndrome.

Palavras-chave:
Anomalias Múltiplas/diagnóstico;
Canal de Libertação de Cálcio do Cecetor de Rianodina;
Doenças Neuromusculares/diagnóstico;
Hipertermia Maligna;
Síndrome.

***Autor Correspondente / Corresponding Author:**
João Galacho Vasco
Avenida D. Manuel I
9500-370 Ponta Delgada, Portugal
jgoncalvesvasco@gmail.com

Recebido / Received: *2023-05-31*
Aceite / Accepted: *2023-10-12*
Publicado / Published: *2023-10-18*

Introduction

The King-Denborough syndrome is a rare congenital myopathy, with a prevalence of 1:1 million, and is associated with susceptibility to malignant hyperthermia, facial dysmorphias, and musculoskeletal abnormalities.[1] Although the etiology of this disease is still unknown, in some cases it has been associated with a mutation in the ryanodine receptor (RYR), present at calcium releasing channel in the skeletal muscle.[2,3-5]

The most common abnormalities are a characteristic facial appearance with palpebral ptosis, micrognathia, and a high-arched palate; concerning the musculoskeletal abnormalities usually present with pectus excavatum, a barrel chest, and lumbar hyperlordosis[5]. Malignant hyperthermia is a rare, potentially lethal, pharmacogenetic syndrome characterized by muscle rigidity, respiratory and metabolic acidosis, and an elevation in body temperature after exposure to inhaled halogenated anesthetics.[3,5,6]

In this report, we describe the first known cases of the King-Denborough syndrome in Portugal and aim to increase awareness of this disease. It is associated with a high lethal reaction, after being exposed to the most common anesthetics used during surgery, which most of these patients are, in their early years of life, due to the musculoskeletal deformities, and can be prevented with a preoperative diagnosis.

Case Report

Here we describe a family with the diagnosis of King--Denborough syndrome (**Fig. 1**), which was first discovered when the youngest child was referred to in--hospital consultation.

We present a 4-year-old girl, born at term, after a pregnancy with inappropriate following, with the first appointment at 32 weeks of gestation. The blood tests and ultrasounds were normal. Birth by elective C-section due to breech presentation. The Apgar score was 1/3/6/10, with need for neonatal resuscitation, due to bradycardia and hypotonia, recovering in the first minutes of life. A constellation of dysmorphias was noted, with low set ears, micrognathism, a high-arched palate, and a left clubfoot. There were no complications during the perinatal period. At 2 months old she was submitted to orthopedic surgery for correction of left clubfoot under general anesthesia without any complication.

In the first pediatric evaluation, at physical examination, it was noted a characteristic facial appearance with bilateral palpebral ptosis, hypomimia, micrognathia, malar hypoplasia, and a high-arched palate. She also presented a bell-shaped chest with pectus excavatum (**Figs. 2 and 3**), lumbar hyperlordosis, short stature and a clubfoot (**Figs. 4 and 5**). At neurological exam presented global hypotonia, proximal muscle weakness and hyporeflexia, a myopathic gait with need for support, and positive Gowers maneuver. Fundoscopy and ocular motricity were normal, there were no pyramidal or extra-pyramidal signs. At development evaluation, she had a normal cognitive development, only with a compromise of motor development.

The hypothesis of myopathy led to several diagnostic tests, with normal creatine kinase, thyroid function and metabolic workup levels. The electromyography was normal, with no muscle fiber lesion and no signs of motor or sensitive polyneuropathy. The requested cerebral magnetic resonance imaging (MRI) showed no abnormal findings. Finally, a NGS panels for hereditary myopathy,

Figure 1. Patient (on the right) with her mother and her brother. Here we can observe the phenotypic similarities between the three members of the family.

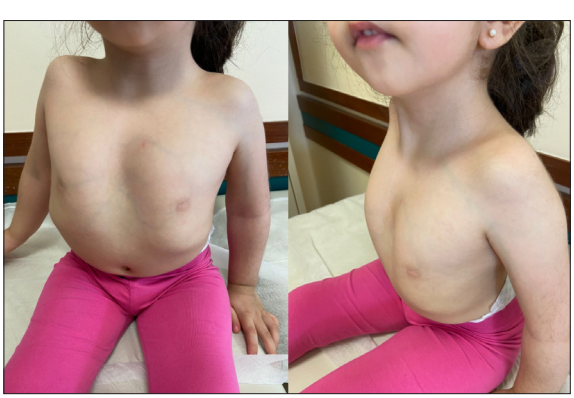

Figure 2 and 3. In these two pictures we find examples of some of the King-Denborough syndrome characteristic findings: malar hypoplasia, micrognathia, pectus excavatum and a barrel-shaped chest.

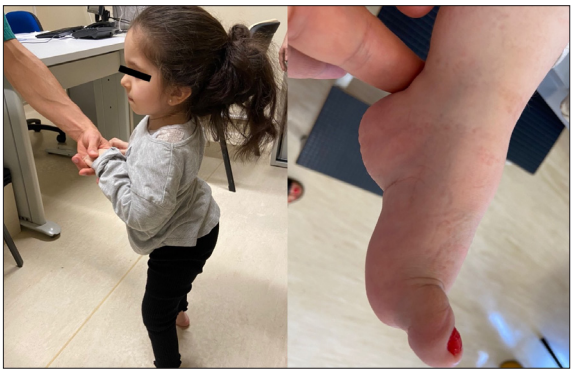

Figure 4 and 5. Here we can notice the marked lumbar hyperlordosis and clubfoot of the patient.

detected a heterozygotic mutation in the *RYR1* gene - (NM_00540.2)-C.7523G>A(p.(Arg.2508His).

There was no history of consanguinity. A 26-years--old mother, with two gestation and no history of fetal loss, presented a very similar facial appearance, lumbar hyperlordosis and a myopathic gait, but lesser motor compromise. Her 11-year-old, mother side half-sibling, was already followed for similar clinical findings, with the same facial characteristics (palpebral ptosis, micrognathia, and low set ears), and also with a bell-shaped chest, lumbar hyperlordosis and bilateral clubfoot, but with normal intellectual development. Later a family genetic test was made and revealed the same heterozygotic variation as the younger sister.

Regarding therapeutic intervention, there is no present pharmacologic intervention for the King-Denborough syndrome, it is a genetic disease and there are no FDA-approved therapeutics for RYR1-related myopathies.[5] Patients with this diagnosis benefit from regular rehabilitation in order to improve motor function and help correct the musculoskeletal abnormalities.

The importance of this diagnostic is that there is a susceptibility to malignant hyperthermia when the patients are exposed to inhaled halogenated anesthetics, which can be fatal and is easily forewarned if other types of anesthetics are used.

At the time of writing, she maintains regular appointments in orthopedics and physical medicine, and motor rehabilitation. The ophthalmologic and cardiac follow--ups were normal. She has a normal cognitive and social score by Griffiths development scale assessment, her gross motor skills have been improving, and nowadays she has autonomous gait with no need for a deambulatory support system.

Discussion

The King-Denborough syndrome was first described in 1972, by King *et al*, who described the case of 4 unrelated children, from Australia and New Zealand, with a slow and progressive myopathy, the same facial characteristics and skeletal deformities. As seen in the patients we described, these boys presented with ptosis, micrognathia, low set years, malar hypoplasia and short stature, and after being subjected to surgery, 3 of them died after a malignant hyperthermia reaction.[6]

Later McPherson *et al*, described a case of a 12-year--old-girl, with a similar phenotype previously described by King *et al*, who after a dental extraction under general anesthesia, died of malignant hyperthermia.[4]

This syndrome has later been related with mutations in the ryanodine receptor 1,[2-4] but is not an exclusive genotype-phenotype syndrome, since it has been associated with other myopathies, most of them with malignant hyperthermia susceptibility, but with different phenotypes.[7]

The family described in this article presents almost all of the distinct characteristics previously described associated with the King-Denborough syndrome. The diagnosis was only possible after the genetic testing, but it could also have been suggested through muscle biopsy. In this syndrome, when abnormal, the biopsy would show a fiber size variation, with increase in connective tissue. The type 1 fibers can vary, in most cases atrophy is noted. Sometimes clear central areas are observed, as in central core disease.[2,3] To note that it was not done in our patient, due to the fact that it is an invasive procedure and it would not be possible to do it in the local hospital, with need to send the child to a specialized center.

The electromyogram (EMG) was normal, what is described in some patients with this syndrome. In some cases, the needle EMG can show myopathic features (short duration, low amplitude, polyphasic motor unit potentials with rapid recruitment; reduced spike duration is described as the most reliable characteristic of myopathy).[8]

About the described genetic mutation, it has been previously identified as a pathogenic variant, linked to central core disease.[9] Although the mother seems to present a less severe clinical phenotype, this is described in the literature, as members of the same family can all have the same mutation and different manifestation of the disease, with a presence of different phenotype with the same genotype.[2,3] In most recent years, with science

advance, some authors start to hypothesize the existence of undiscovered heterozygotic mutations even between same family members, what could explain the genotype-phenotype variety.[2,9]

This report aims to bring attention to the proper work-up study and to persist investigation with genetic testing, when the diagnosis of a congenital myopathy is highly probable. The new era of molecular biology advances has proven to be of crucial importance, in cases of difficult diagnosis. Furthermore, we want to reinforce that in cases that need an early surgical intervention, the recognition of syndromes associated with malignant hyperthermia is of extreme importance, since it is a mostly fatal reaction, that can be easily avoided. ■

Contributorship Statement / Declaração de Contribuição
JV: Manuscript elaboration.
EV, PP: Manuscript review.
All authors approved the final version to be published.

Responsabilidades Éticas
Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Consentimento: Consentimento do doente para publicação obtido.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures
Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship. Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Patient Consent: Consent for publication was obtained.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Reed UC, Resende MB, Ferreira LG, Carvalho MS, Diament A, Scaff M, Marie SK. King-Denborough Syndrome: report of two Brazilian cases. Arq Neuropsiquiatr. 2002;60:739-41. doi: 10.1590/s0004-282x2002000500011.
2. Dowling JJ, Lillis S, Amburgey K, Zhou H, Al-Sarraj S, Buk SJ, et al. King-Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (RYR1) gene. Neuromuscul Disord. 2011;21:420-7. doi: 10.1016/j.nmd.2011.03.006.
3. D'Arcy CE, Bjorksten A, Yiu EM, Bankier A, Gillies R, McLean CA, Shield LK, Ryan MM. King-denborough syndrome caused by a novel mutation in the ryanodine receptor gene. Neurology. 2008;71:776-7. doi: 10.1212/01.wnl.0000324929.33780.2f.
4. McPherson EW, Taylor CA Jr. The King syndrome: malignant hyperthermia, myopathy, and multiple anomalies. Am J Med Genet. 1981;8:159-65. doi: 10.1002/ajmg.1320080206.
5. Lawal TA, Todd JJ, Meilleur KG. Ryanodine Receptor 1-Related Myopathies: Diagnostic and Therapeutic Approaches. Neurotherapeutics. 2018;15:885-99. doi: 10.1007/s13311-018-00677-1.
6. King JO, Denborough MA, Zapf PW. Inheritance of malignant hyperpyrexia. Lancet. 1972;1:365-70. doi: 10.1016/s0140-6736(72)92854-1.
7. Wedel DJ. Malignant hyperthermia and neuromuscular disease. Neuromuscul Disord. 1992;2:157-64. doi: 10.1016/0960-8966(92)90001-m.
8. Shanina E, Smith RG. Electrodiagnostic Evaluation of Myopathy. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022. [accessed Jan 2023] Available from: https://www.ncbi.nlm.nih.gov/books/NBK564383/
9. Wu S, Ibarra MC, Malicdan MC, Murayama K, Ichihara Y, Kikuchi H, et al. Central core disease is due to RYR1 mutations in more than 90% of patients. Brain. 2006;129:1470-80. doi: 10.1093/brain/awl077.