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KING-DENBOROUGH SYNDROME

Report of two Brazilian cases

Umbertina Conti Reed[1], Maria Bernardete Dutra Resende[2] Lúcio Gobbo Ferreira[2], Mary Souza Carvalho[3], Aron Diament[1], Milberto Scaff[4], Suely Kazue Nagahashi Marie[1]

ABSTRACT - We report on two boys aged 2 and 6 years-old respectively with dysmorphic face, ptosis, down-slanting palpebral fissures, hypertelorism, epicanthic folds, low-set ears, malar hypoplasia, micrognathia, high-arched palate, clinodactyly, palmar simian line, pectus excavatum, winging of the scapulae, lumbar lordosis and mild thoracic scoliosis who present congenital hypotonia, slightly delayed motor development, diffuse joint hyperextensibility and mild proximal weakness. The muscle biopsy revealed minimal but identifiable changes represented by size fiber variability, type I fiber predominance and atrophy, perimysial fibrous infiltration and some disarray of the intermyofibrillary network. These cases correspond to the first Brazilian reports of the King-Denborough syndrome and our objective is increasing the awareness of this disorder as these patients are predisposed to developing malignant hyperthermia.

KEY WORDS: King-Denborough syndrome, congenital myopathy, malignant hyperthermia.

Síndrome de King-Denborough: relato de dois casos

RESUMO - Relatamos dois meninos de 2 e 6 anos de idade que apresentam aspectos dismórficos caracterizados por facies alongada, ptose e fenda palpebral anti-mongólica, hipertelorismo, epicanto bilateral, orelhas de implantação baixa, hipoplasia malar, micrognatia, pálato ogival, clinodactilia, prega palmar única, "pectus excavatum", escápulas aladas, lordose lombar e escoliose torácica. Apresentam hipotonia congênita, hiperextensibilidade articular, fraqueza muscular e retardo do desenvolvimento motor. A biópsia muscular revelou em ambos alterações mínimas: variabilidade do tamanho das fibras, predomínio e atrofia de fibras tipo I, discreta infiltração perimisial e desarranjo intermiofibrilar. Os aspectos dismórficos associados à miopatia congênita configuram a síndrome de King-Denborough, da qual acreditamos serem estes os primeiros casos descritos no Brasil. Como a síndrome se acompanha de alto risco de desenvolver hipertermia maligna na indução anestésica, o objetivo deste relato é chamar a atenção para a necessidade do diagnóstico pré-operatório, a fim de evitar esta gravíssima intercorrência.

PALAVRAS-CHAVE: síndrome de King-Denborough, miopatia congênita, hipertermia maligna.

The King-Denborough syndrome (KDS) is a congenital myopathy associated with susceptibility to malignant hyperthermia (MH), skeletal abnormalities and dysmorphic features with characteristic facial appearance[1-5].

We present the first report in Brazil concerning two KDS patients and as these children are predisposed to developing MH, our objective is increasing the awareness of this disorder. Considering the severity and the high rate of lethality of a MH reaction, as children with KDS are likely to undergo surgery with general anesthesia for cryptorchidism and skeletal deformities, a preoperative diagnosis should be recognized.

CASES

Case 1. A one-year-old boy was born at term following an uneventful pregnancy from non consanguineous parents and presented from birth congenital hypotonia, ptosis and dysmorphic face. Motor development was moderately delayed and the child acquired independent walking at 19 months of age. Language and mental development were normal. Our first examination at 12 months of age revealed marked ptosis, down-slanting palpebral fissures, hypertelorism, epicanthic folds, malar hypoplasia, micrognathia, high-arched palate, clinodactyly, pectus excavatum, lumbar lordosis and cryptorchidism (Fig 1). At neurological examination we observed normal mental develpment, nor-

Department of Neurology, Clínicas Hospital, School of Medicine, University of São Paulo, São Paulo SP, Brazil: [1]Associate Professor; [2]Post Graduate Student; [3]Assistant Professor; [4]Full Professor and Chairman.

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Dr. Umbertina Conti Reed - Departamento de Neurologia, Faculdade de Medicina (USP) - Avenida Dr. Arnaldo 455/4110 - 01246-903 São Paulo SP - Brasil. FAX 55 11 3061-4036, 55 11 3742-2340. E-mail address: ucontireed@hcnet.usp.br

mal muscular strength, diffuse muscular hypotonia and joint hyperextensibility, as well as hypoactive deep tendon reflexes. Ocular motility was normal. Serum creatine kinase levels were normal and electromyography revealed abnormal myopathic pattern of muscle discharges. The muscle biopsy revealed minimal changes represented by size fiber variability, perimysial fibrous infiltration and some round fibers There was no disarray of the intermyofibrillary network. After a follow-up of 15 months the course is stable and the child shows minimal motor disability.

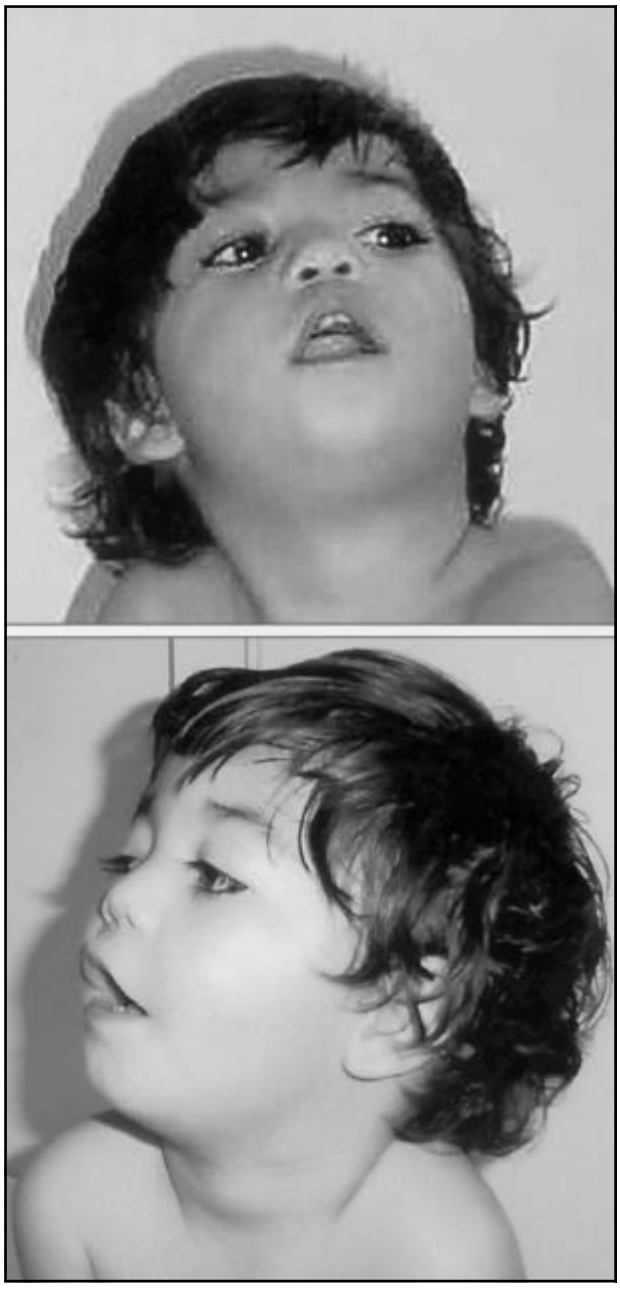

Fig 1. Patient 1 at 21 months. Note the dysmorphic changes: ptosis, down-slanting palpebral fissures, hypertelorism, malar hypoplasia and micrognathia. (Photo authorized by the legal responsible).

Case 2. A 6-year-old male was born at term following an uneventful pregnancy from non consanguineous parents and presented from birth congenital hypotonia and weakness, ptosis, dysmorphic face, and scoliosis. The neonatal period was complicated by poor sucking and failure-to-thrive. Motor development was moderately delayed but language and mental development were normal. Cryptorchidopexy was performed at 3 years of age out of our institution without complications but it was not possible to confirm which anesthetics were utilized. Our first examination at 6 years of age revealed elongated face with marked ptosis, down-slanting palpebral fissures, hypertelorism, epicanthic folds, low-set ears, malar hypoplasia, micrognathia, high-arched palate, clinodactyly, palmar simian line, pectus excavatum, winging of the scapulae, lumbar lordosis and mild thoracic scoliosis. Neurological examination showed normal intelligence. Weakness was mild showing proximal predominance in the upper extremities and diffuse distribution in the lower extremities. Muscular hypotonia and joint hyperextensibility were diffuse and moderate, and deep tendon reflexes were hypoactive. A mild bilateral facial weakness was noted and ocular motility was normal. Serum creatine kinase levels and electromyography were normal. The muscle biopsy revealed minimal but identifiable changes represented by size fiber variability, type I fiber predominance and atrophy, perimysial fibrous infiltration and some disarray of the intermyofibrillary network. Cardiac evaluation was normal. After a follow-up of 27 months the course can be considered stable and the child is attending a normal school with minimal disability. A test for MH susceptibility will be scheduled as soon as patient's age allows and possibly in their family members who live 2000 Km faraway from our institution.

DISCUSSION

King et al.[1] described 4 unrelated children from Australia and New Zeland with a slowly progressive myopathy, as well as ptosis, short stature, low-set ears, malar hypoplasia, skeletal deformities, and cryptochirdism[1]. All patients were boys and had been diagnosed after episodes of malignant hypertermia, in which three died. The presence of a myopathy associated with a predisposition to malignant hyperthermia suggests an autosomal dominant pattern of inheritance with variable expression. Our patients had most of the characteristic phenotypical aspects, although unlike other reported cases, they had normal height and did not manifest dental crowding / malocclusion. As there is some phenotypic overlap between the King and Noonan syndromes, the latter a multiple congenital anomaly syndrome inherited in an autosomal dominant pattern, a genetic relationship between the two syndromes has been supposed[5]. However, Noonan syndrome, that was already reported in Brazilian children[7-9], is not associated

with myopathic changes and presents characteristic heart defect in 65% of the patients. The definition that King and Noonan syndromes may represent allelic autosomal dominant entities or be independent and linked to separate loci, depends on further molecular studies[5]. It has also been proposed that the King syndrome represents a common phenotype that may result from several different slowly progressive congenital myopathies[6]. It is our opinion that despite the clinical phenotype of an underlying myopathy, the rarity of the syndrome among children with congenital myopathies of different types and the typical dysmorphic changes point to a specific genetic defect not yet detected. Apparently there is no linkage to any of the already identified MH locus, so indicating the genetic heterogeneity of MH.

We recommend to evaluate all patients with clinical signs consistent with KDS and their relatives prior to anesthesia. It would be also useful to investigate the possibility of a subclinical myopathy in patients diagnosed as Noonan syndrome not only for emphasizing the risk, although minimal of MH, but also as a contribution for defining or not the individuality of the two syndromes.

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