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Case Report

Congenital neurogenic muscular atrophy in megaconial myopathy due to a mutation in *CHKB* gene

Manuel Castro-Gago [a], David Dacruz-Alvarez [a], Elena Pintos-Martínez [b], Andrés Beiras-Iglesias [b], Joaquín Arenas [c,d], Miguel Ángel Martín [c,d], Francisco Martínez-Azorín [c,d,*]

[a] *Servicio de Neuropediatría, Departamento de Pediatría, Hospital Clínico Universitario, Facultad de Medicina, Santiago de Compostela, Spain*
[b] *Servicio de Anatomía Patológica, Hospital Clínico Universitario, Facultad de Medicina, Santiago de Compostela, Spain*
[c] *Laboratorio de Enfermedades Mitocondriales, Instituto de Investigación Hospital 12 de Octubre (i+12), E-28041 Madrid, Spain*
[d] *Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), U723, E-28041 Madrid, Spain*

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Abstract

Choline kinase beta gene (*CHKB*) mutations have been identified in Megaconial Congenital Muscular Dystrophy (MDCMC) patients, a very rare inborn error of metabolism with 21 cases reported worldwide. We report the case of a Spanish boy of Caucasian origin who presented a generalized congenital muscular hypotonia, more intense at lower limb muscles, mildly elevated creatine kinase (CK), serum aspartate transaminase (AST) and lactate. Electromyography (EMG) showed neurogenic potentials in the proximal muscles. Histological studies of a muscle biopsy showed neurogenic atrophy with enlarged mitochondria in the periphery of the fibers, and complex I deficiency. Finally, genetic analysis showed the presence of a homozygous mutation in the gene for choline kinase beta (*CHKB*: NM_005198.4:c.810T>A, p.Tyr270*). We describe here the second Spanish patient whit mutation in *CHKB* gene, who despite having the same mutation, presented an atypical aspect: congenital neurogenic muscular atrophy progressing to a combined neuropathic and myopathic phenotype (mixed pattern).

Keywords: *CHKB*; Megaconia; Muscular dystrophy; Neurogenic; Muscular atrophy; Mitochondria

1. Introduction

The choline kinase beta enzyme (EC 2.7.1.32) catalyzes the first step of phosphatidylcholine (PC) biosynthesis and it is encoded by the choline kinase beta gene (*CHKB*; MIM #612395). Mutations in this gene may result in loss of choline kinase activity and decreased levels of PC, and it was hypothesized that altered phospholipid composition in muscle mitochondrial membrane may lead to mitochondrial structural and functional abnormalities [1].

Only 21 patients (4 Japanese [2], 10 Turkish [3], 3 British [4], 1 French [5], 1 African-American [6], 1 Spaniard [7] and 1 Italian [8]) with mutations in the *CHKB* gene have been characterized and published. In all these cases, the loss-of-function mutations in *CHKB* [9] produced Megaconial Congenital Muscular

* Corresponding author at: Laboratorio de Enfermedades Mitocondriales, Instituto de Investigación Hospital 12 de Octubre (i+12), Centro de Actividades Ambulatorias (CAA), 6ª Planta, Bloque E, Avda. Córdoba s/n, E-28041 Madrid, Spain. Tel.: +34 91 779 2784; fax: +34 91 390 8544.
E-mail address: fmartinez@h12o.es (F. Martínez-Azorín).

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Dystrophy (muscular dystrophy, congenital, with Mitochondrial Structural Abnormalities, MDCMC; MIM #602541) that is characterized clinically by early-onset hypotonia, muscle wasting, mildly elevated serum creatine kinase (CK) levels, and severe intellectual disability without brain structural abnormalities [2]. Muscle biopsies in these patients reveal mitochondrial abnormalities that seem to be specific to this disease: the center of the muscle fibers is depleted of mitochondria, whereas at the periphery the mitochondria are markedly enlarged (megaconia or megamitochondria) [2]. Weakness is predominantly proximal and slowly progressive and cardiomyopathy is often a cause of morbidity and mortality [3].

Here, we describe the second Spanish patient with the same nonsense mutation in *CHKB* gene that the previously reported. However, this patient presents a congenital neurogenic muscular atrophy (evolving to neurogenic/myopathic phenotype) instead of a congenital myopathic muscular dystrophy.

2. Case report

An 11-month-old Spanish boy (Caucasian origin) was referred to our center for presenting hypotonia. He was the first child of a young non-consanguineous couple without relevant family history. He was born after a normal pregnancy and delivery, and his neonatal period was uneventful. Newborn screening test for metabolic disorders was normal and he was properly vaccinated. However, the family noticed muscle weakness from 4 months of age and he could not roll over on cot. He reached affective smile between 3 and 4 months of age and cephalic tone at 8 months of age. On examination, he showed a generalized hypotonia more intense at lower limb muscles. On vertical suspension, he slipped through the examiner's hands. He was not able to sit without support until 2-year-old. He has the fontanelle punctiform, decreasing myotatic reflexes and absence of organ enlargement, absence of tongue fasciculations and absence of any other special phenotypic traits. MRI imaging of the brain was normal.

In complementary examination, the creatine kinase (CK) and aspartate transaminase (AST) levels were mildly elevated in serum (239 IU/L, normal: 15–110 IU/L, and 40 IU/L, normal: 0–25 IU/L, respectively). Serum lactate (2.42 mM, normal: 0.33–1.33 mM) and pyruvate levels (0.16 mM, normal: 0.03–0.08 mM) were also increased. Serum acylcarnitine profile and urine guanidinoacetic acid and creatine levels were normal. At 1-year-old, electroneurography (ENoG) showed normal motor and sensory nerve conduction velocities (Table 1). Electromyography (EMG) showed spontaneous fibrillation potentials and positive waves (a characteristic of neurogenic disease in the absence of muscle inflammation and necrosis), in right deltoid and right vastus lateralis muscles. However, under activation of the muscle fibers (difficult by the patient's age) normal patterns were observed in the muscles explored (Table 2). At 4 years-old, the cardiac evaluation and auditory brainstem responses were normal.

Table 1
Electroneurography (ENoG).

	1 year old	4.5 years old
Motor nerve conduction		
Median right (wrist–elbow)		
Latency (ms)	3.8	nd
Amplitude (mV)	4.9	nd
CV (m/s)	45.9	nd
Tibial right (ankle–popliteal)		
Latency (ms)	5.3	nd
Amplitude (mV)	6.4	nd
CV (m/s)	42.6	nd
Tibial left (ankle–popliteal)		
Latency (ms)	5.4	5.9
Amplitude (mV)	6.5	10.6
CV (m/s)	38.5	53.0
Peroneal right (ankle–fibula head)		
Latency (ms)	nd	5.9
Amplitude (mV)	nd	8.7
CV (m/s)	nd	49.0
Sensory nerve conduction		
Sural left (sural)		
Amplitude (μV)	5.6	29.0
CV (m/s)	36.2	49.0
Sural right (sural)		
Amplitude (μV)	7.9	nd
CV (m/s)	36.2	nd
Median right (wrist)		
Amplitude (μV)	24.6	nd
CV (m/s)	38.7	nd

nd: not done.

Table 2
Electromyography (EMG).

Nerve	1 year old	4.5 years old
Vastus lateralis right		
Fibrillation potential	Positive	Positive
Positive waves	Positive	Positive
Motor unit potentials	Normal	Normal
Tibialis anterior right		
Fibrillation potential	Negative	Negative
Positive waves	Negative	Negative
Motor unit potentials	Normal	Normal
Deltoid right		
Fibrillation potential	Positive	Negative
Positive waves	Negative	Negative
Motor unit potentials	Normal	Myopathic[1]
Extensor digitorum right		
Fibrillation potential	Negative	nd
Positive waves	Negative	nd
Motor unit potentials	Normal	nd
Biceps right		
Fibrillation potential	nd	Negative
Positive waves	nd	Negative
Motor unit potentials	nd	Myopathic[1]

nd: not done.
[1] Myopathic: areas of low amplitude and increased polyphase.