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LETTER TO THE EDITOR Open Access

Some DNM2 mutations cause extremely severe congenital myopathy and phenocopy myotubular myopathy

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Centronuclear myopathies (CNM) are rare congenital myopathies characterized by muscle weakness with facial and eye involvement and intracellular disorganisation of myofibers with centralized nuclei [5, 8]. Several forms and mode of inheritance have been described. The most severe form, also called X-linked myotubular myopathy, is due to *MTM1* mutations and is associated with perinatal severe hypotonia and respiratory distress leading to death of most affected boys in infancy (MIM#310400) [7]. Dominant *DNM2* mutations are linked to milder cases with either neonatal, childhood or adult onset and proximal or diffuse muscle weakness (MIM#160150) [2, 3]. Previously described neonatal *DNM2* cases showed gradual improvement in motor function and survival into adulthood [1]. Unlike *MTM1*-CNM, reported cases of *DNM2*-CNM biopsies often show a radial distribution of sarcoplasmic strands on cross sections. Here we present three unrelated *DNM2*-CNM cases resembling myotubular myopathy at the clinical and histopathological levels.

Two girls and one boy from unrelated families presented at birth with global and severe hypotonia with respiratory distress requiring invasive and permanent respiratory support (Additional file 1: Table S1). Patients 1 and 2 had multiple contractures. Patient 1 is a male born at 29 weeks of estimated gestational age (EGA), presenting with foetal akinesia and disturbance of cardiac rhythm. Hydramnios was detected. He had a congenital and bilateral chylothorax and died at 5 weeks from a bronchopulmonary dysplasia. Patient 2 is a girl delivered at term by cesarean section due to monotonic heart rate. No amniotic fluid was present. She presented with small intracerebral hemorrhages but no major brain malformations at 1.5 months, and developed 40 degrees convex scoliosis by 4 months. Extubation attempt at 5 months failed and she died at 8 months of age from pneumonia. Patient 3 is a girl born at 34 weeks of EGA. She had a bilateral ptosis and high-arched palate. Brain MRI uncovered a leukoencephalopathy with enlarged ventricles and reduced white matter. She died at 4 months from respiratory failure.

Muscle biopsies were performed at 1 month from quadriceps for patients 1 and 3 and at autopsy at 8 months for patient 2. They showed fiber size variability and hypotrophic muscle fibers with prominent nuclear centralizations (Fig. 1a). No clusters of nuclei were observed (Additional file 1: Figure S1). NADH-TR staining revealed centrally located hyperintense reaction in the majority of fibers, without radial distribution of sarcoplasmic strands as the spokes of a wheel. Predominance of type 1 fiber was observed for patient 2 with more variability in fiber size and some increase in connective tissue. Electron microscopy ultrastructural analysis in patient 1 confirmed the presence of prominent nuclear centralizations. Of note centralized nuclei were surrounded by amorphous material and partially disorganized and misaligned sarcomeres. Satellite cells count appeared normal unlike neonates with myotubular myopathy in whom a decrease was noted [9](Fig. 1b).

MTM1 mutations were excluded in patients 1 and 3. All the patients were found with heterozygous de novo *DNM2* mutations, NM_001005360.2: c.1831G > A -

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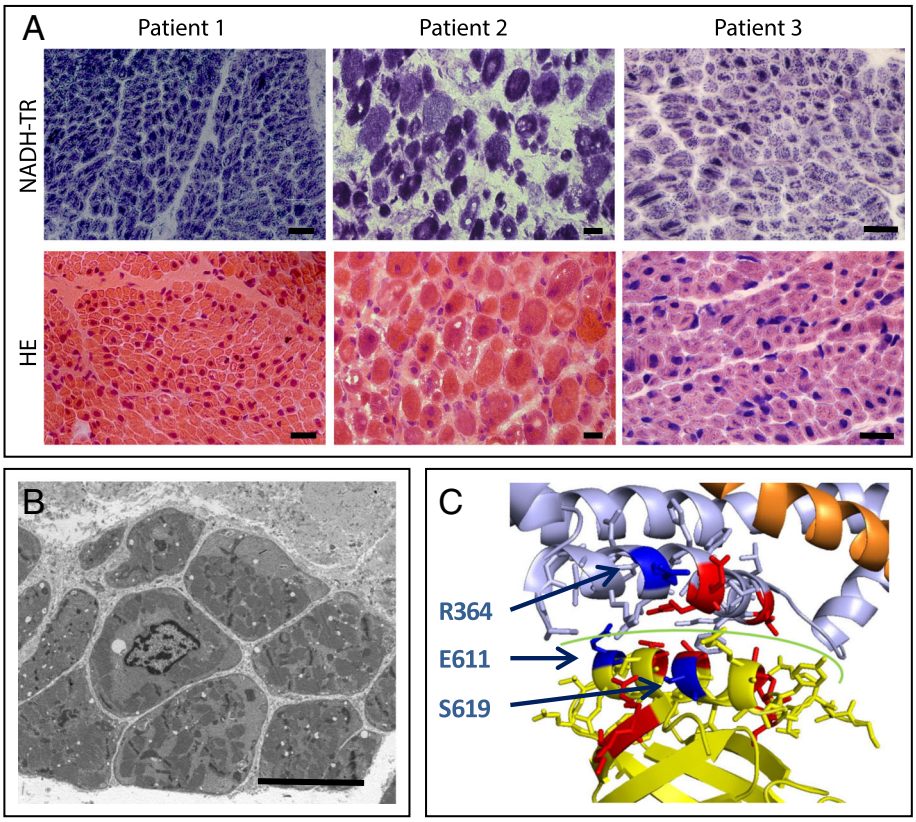

Fig. 1 a. Hematoxilin-eosin (HE) and nicotinamide adenosine dinucleotide-tetrazolium reductase (NADH-TR) staining of muscles from the patients, showing fibers with centralized nuclei (HE) and abnormal central accumulation oxidative staining and a paler peripheral halo. Scale bars 20 μm. **b.** Electron microscopy of patient 1 muscle showing partial sarcomeres disorganisation and central nuclei. Scale bar 10 μm. **c.** Localization of presently reported mutations (dark blue) compared to known *DNM2*-CNM mutations (red) on the 3D model of nucleotide-free human DNM1 (PDB 3SNH). They all clusterize at the PH (yellow) – Middle/stalk (light blue) interface (green line)

p.Glu611Lys, c.1090C > T - p.Arg364Cys, and c.1856C > T - p.Ser619Leu for patient 1, 2 and 3 respectively, through direct Sanger sequencing or an arthrogryposis gene panel (CeGaT, Tübingen, Germany). The p.Ser619Leu mutation was reported in at least 11 CNM cases with neonatal onset and a milder course compared to the present cohort. Mutations p.Glu611Lys and p.Arg364Cys are novel and are not found in gnomAD (http://gnomad.broadinstitute.org/). They affect aminoacids conserved down to drosophila and are predicted pathogenic by SIFT and Polyphen-2. Furthermore, they cluster with most known mutations on the 3D structure (Fig. 1c).

Here we report the most severe CNM patients with heterozygous *DNM2* mutations. Compared to previously reported *DNM2*-CNM cases [3], they were fully dependent on invasive ventilation and all died within the first months of life. The very early lethal outcome in patient 1 may have been influenced by concomitant prematurity. Nevertheless, the three patients did not improve except for a slight muscle strength enhancement appearing after 6 months of age in patient 2. Furthermore, early developmental milestones were delayed (Additional file 1: Table S1), in contrast with some previously described neonatal onset *DNM2* patients [4]. This study enlarges the clinical and genetic spectrum of *DNM2*-CNM. Moreover, it underlines that *DNM2* mutations can be associated with decreased survival.

In addition to a CNM phenotype, the 3 patients display similar features with the lethal congenital contracture syndrome (MIM#615368) due to a *DNM2* homozygous mutation [6], especially multiple contractures, fetal hypokinesia, pulmonary hypertension, brain hemorrhages, and abnormal fetal heart rythm.

The present *DNM2*-CNM cases were highly similar to myotubular myopathy due to *MTM1* mutations, although none of them presented with the association of facial hypotonia, ptosis, ophthalmoplegia and elongated face that is typical in *MTM1*-CNM cases. In addition to the perinatal severity, they had very severe hypotonia, respiratory distress and the same histopathological findings, lacking the radial strands hallmark of most other *DNM2* cases.

In conclusion, *DNM2* should be investigated in congenital myopathies presenting as myotubular myopathy.

Additional file

Additional file 1: Clinical, molecular, histopathological and ultrastructural findings for the patients. **Table S1** Clinical and molecular findings in the *DNM2* severe cases. **Figure S1** Histopathological and ultrastructural findings for the patients. Patients 1, 2 and 3: Hematoxilin-eosin (HE) staining of muscles showing fibers with centralized nuclei. Patient 1: ATPase at pH 9.4 showing type I (pale) and type II (dark) fibers. Patient 3: ATPase at pH 4.6 showing type 1 fibers dark and type 2 fibers less stained. Scale bars 20 μm. (ZIP 46909 kb)

Abbreviations

CNM: Centronuclear myopathies; DNM2: Dynamin 2; EGA: Estimated gestational age; HE: Hematoxilin-eosin; MRI: Magnetic resonance imaging; MTM1: Myotubularin 1; NADH-TR: Nicotinamide adenine dinucleotide tetrazolium reductase

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Availability of data and materials

All data generated or analysed during this study are included in this published article [and its Additional files].

Authors' contributions

VB, NBR, AO and JL directed the study; IJT, JK and DH performed clinical examination; NBR, EM, MG and AO performed histological examinations; VB and JL analyzed the data and wrote the manuscript with input from other authors. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Competing interests

The authors declare that they have no competing interests.

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