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<th><strong>Title</strong></th>
<th>Congenital myopathies: characteristic and subtypes in Hong Kong</th>
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Background: Congenital myopathies (CMs) are a genetically and clinically heterogeneous group of neuromuscular disorders. Historically, the congenital myopathies are classified according to muscle biopsy findings — rods (Nemaline myopathy) (NM), cores (central core disease and multiminicores disease) (Core and MMC: core and multiminicores myopathy) (CNM), and selective hypotrophy of type I fibres (congenital fibre type disproportion) (CFD). Over twenty genes have been implicated in CMs. The overlapping clinical presentations among different histopathological findings and different mutations poses major diagnostic challenge.

Objective: We investigated the characteristics of children with congenital myopathies in Hong Kong.

Patients and methods: We identified all patients with a confirmed diagnosis of CM between 2012-March 2015. Their clinical presentation, muscle biopsy, muscle MRI and genetic analysis results were evaluated.

Results: Patients: Total 15 patients have been diagnosed to have CM. Nine were males (60%), 6 were females (40%).

Genetic findings: (1) A genetic diagnosis could be established in 11 (73%) out of 15 patients. Among those 11 patients, 4 (36%) were mutated in RYR1, 3 (27%) in ACTA1, 2 (18%) in KLHL40, 1 (9%) in MYH7, and 1 (9%) in DNM2. A total of 13 mutations were identified.

(2) The missense RYR1 mutation (c.3523G>A) was found in 2 patients, and the missense KLHL40 mutation (c.1516A>C) was found in another 2 patients, suggesting that these variants could probably be the hot spots mutation among Chinese patients.

Pathological heterogeneity caused by RYR1 mutation is shown in our 4 patients showing different findings including nemaline rods, central cores, multiminicores, or type I fibre predominance.

Histopathological features: (1) Muscle biopsy evaluation were available in all 15 patients. Nemaline myopathy was the most frequent histopathological diagnosis, in 9 patients (60%), followed by core myopathy, in 4 patients (26%), centronuclear myopathy in 2 patients (13%), congenital fibre type disproportion in 2 patients (13%), zebra fibres in 1 (6.7%) patient and type I predominance in 1 (6.7%) patient.

(2) Genetic heterogeneity is illustrated in our patients with nemaline myopathy. Amongst the 5 patients, 1 had RYR1, 2 had ACTA1 and 2 had KLHL40 mutation.

Clinical features: (1) Of the 15 patients, 9 (60%) had age of onset at birth or before one month, 3 (20%) between 1 and 12 months, and 3 (20%) between 1 and 5 years. Out of the 9 patients with early neonatal presentation, 3/9 (33%) patients died before 15 months.

(2) The functional abilities varied from very severe weakness required tube feeding and ventilation support, to intermediate functional abilities with possible independent sitting, to mild limb girdle weakness only.

(3) ACTA1, KLHL40, DNMM and MTM1 mutations are associated with severe presentation with early neonatal onset.

(4) RYR1 mutations are associated with a milder phenotype with all the affected patients maintain independent walking.

Muscle imaging: Selective muscle involvement with Rrectus Femoris sparing provides helpful clues to a possible underlying RYR1 mutation.

References:

(a b) Electron microscopy (EM) of muscle biopsies of patients 4 & 5 with nemaline myopathy due to KLHL40 mutation with roundish rods (cdk). Electron microscopy of muscle biopsies of patient 2 & 3 with nemaline myopathy due to ACTA1 mutation; (c) Muscle biopsy of patient 12 with central core disease having rods shown on EM; (f) A zebra body is noted on the EM of patient 7 with ACTA1-related congenital myopathy when the muscle biopsy was performed at 1.5 months old; (g & h) Muscle biopsy of patient 15 with multi-minicores on the EM; (i & j) Muscle biopsy of patient 8 with multi-minicores disease due to RYR1 mutation showing uneven staining with SDH in some fibres and EM shows a large minicone with excess Z-line material and myofilament disruption; (k & l) Muscle biopsy of patient 7 with central core myopathy due to RYR1 mutation with NADH shows numerous cores and EM shows a central core in the centre with disrupted Z-line. (m & n) Muscle biopsy of patient 11 with centronuclear myopathy due to DNM2 mutation. Central nuclei are seen in some fibres (H&E) and no radiating strands are noted from the central nuclei (NADH).