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Congenital myopathies : characteristics and subtypes in Hong Kong

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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 multiminicore disease) (Core and MMC), central nuclei (centronuclear/ myotubular myopathy)(CNM) , and selective hypotrophy of type 1 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 female (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 *MTM1* and 1 (9%) in *DNM2*. A total of 13 mutation 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.

(3) Pathological heterogeneity caused by *RYR1* mutation is shown in our 4 patients showing different findings including nemaline rods, central cores, multiminicores, or type 1 fibre predominance.

Histopathological features:

(1) Muscle biopsy evaluation were available in all 15 patients. Nemaline myopathy were the most frequent histopathological diagnosis, in 5 patients (33%), followed by core myopathy, in 4 patients (26%), centronuclear myopathy in 2 patients (13%), congenital fibre type disproportion in 2 patients (13%), zebra bodies in 1 (6.7%) patient and type 1 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 13 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, DNM2* 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 Rectus Femoris sparing provides helpful clues to a possible underlying RYR1 mutation.

References:

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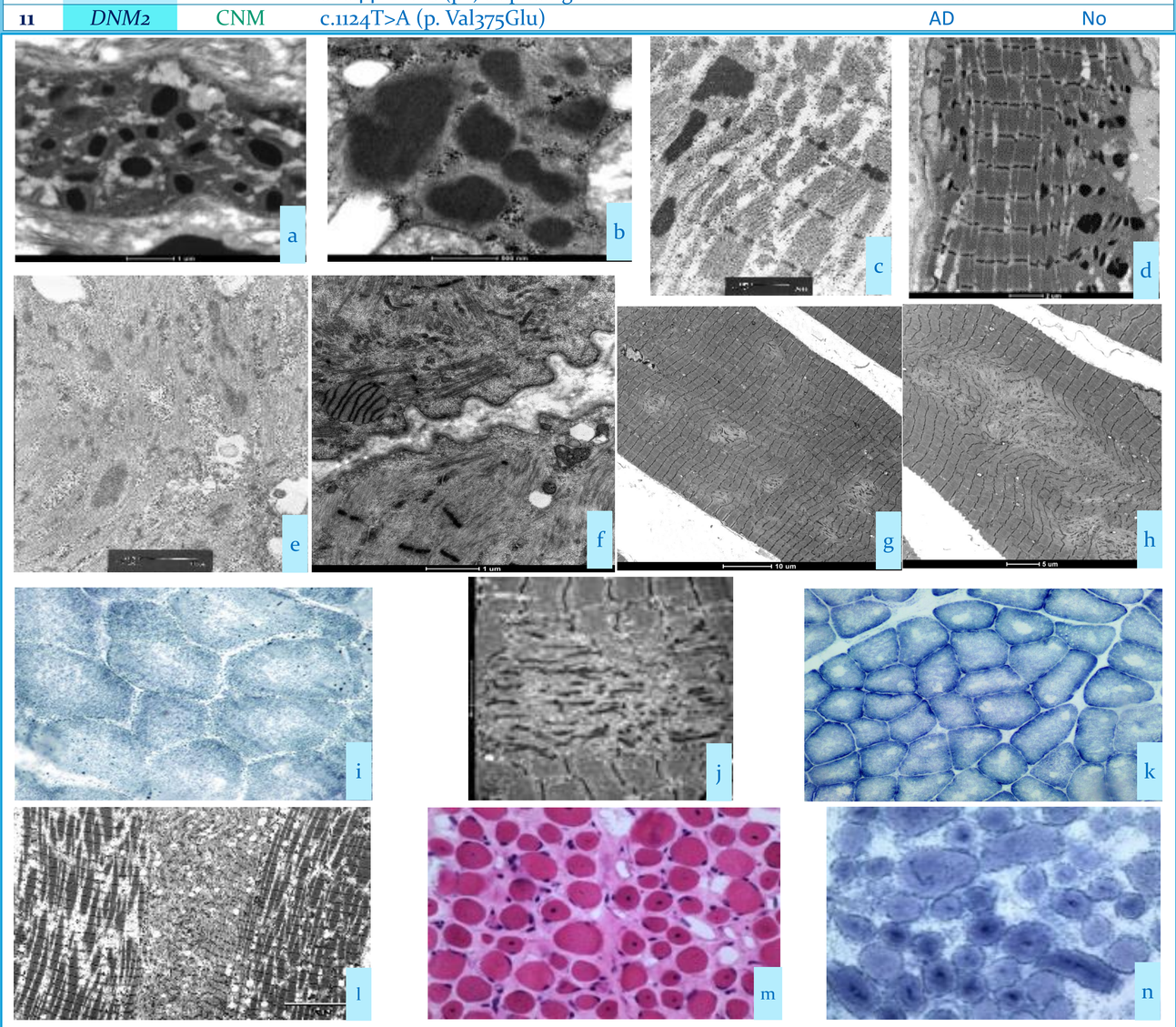
	Gene	M. biopsy	Sex	Onset	Age	Motor Fn	Initial sign or symptom	EOM	Bul -bar	IV/ NIV	Tube/ PEG feeding
1	*ACTA1*	ZB	M	< 1wk	*Died 13 m*	Lyer	Weakness+++	-	+	NIV	PEG
2	*ACTA1*	NM	M	1m	7 y	Sitter (S)	Floppy baby	-	+	NIV	PEG
3	*ACTA1*	NM	F	<1m	11 m	Lyer	Weakness +++	-	+	NIV	PEG
4	*KLHL40*	NM	F	Birth	*Died 7 m*	Lyer	Weakness +++	+	+	IV	TF
5	*KLHL40*	NM	M	Birth	9.5 m	Lyer	Weakness	+	+	NIV	PEG
6	*RYR1*	NM	F	<1	11.8 y	Walker	Unsteady gait	+	-	-	+ → oral
7	*RYR1*	Core	M	<5	20 y	Walker	Tip toe walking	-	-	-	-
8	*RYR1*	MMC	M	<1	4.7 y	Walker	Floppy baby	-	-	-	-
9	*RYR1*	TIP	F	<1	22.7 y	Walker	Floppy baby	-	-	-	-
10	*MTM1*	CNM	M	Birth	17 y	Sitter (S)	Weakness+++	+	-	+	+ → oral
11	*DNM2*	CNM	M	<1m	*Died 10 m*	Lyer	Floppy baby		+	-	+ → oral
12	*	C & R	M	Birth	22 y	Sitter	Weakness+++	-	+	NIV	PEG
13	Pending	MMC	M	<5	14.1 y	Walker	Clumsiness	-	-	-	-
14	**	CFD	F	<3 m	4 y	Walker (S)	Floppy baby	+	-	-	-
15	Pending	CFD	F	1.5y	24 y	Sitter	Delay walking	-	-	+	-

* No mutation found *in RYR1, ACTA1, SEPN1, KBTBD13;* ** No mutation found in *RYR1, ACTA1, SEPN1, TPM2, TPM3*; (S) – supported; ZB: zebra bodies; NM: Nemaline myopathy; Core and MMC: core and multiminicore myopathy; CNM: centronuclear myopathy; CFD: congenital fibre type disproportion; TIP: type 1 disproportion; C&R; cores and rods; Motor Fn: Motor function; EOM: extraocular muscles involvement; IV/ NIV: invasive ventilation/ non-invasive ventilation; PEG: Gastrostomy

	Gene	Muscle biopsy	Mutation	Inheritance Pattern	Parents' carrier status
1	*ACTA1*	ZB	c.529A>G (p.Ile177Val)	AD	No
2	*ACTA1*	NM	c.802T>C (p.Phe268Leu)	AD	No
3	*ACTA1*	NM	c.547G>A (p.Ala183Thr)	AD	No
4	*KLHL40*	NM	c.1516A>C(p.Thr506Pro)	AR	Yes
5	*KLHL40*	NM	c.1327G>A(p.Gly443Ser) + c.1516A>C(p.Thr506Pro)	AR	Yes
6	*RYR1*	NM	c.3800C>G (p.Pro1267Arg) + c.1675dup (p.Ile559Asnfs*11)	AD	Yes
7	*RYR1*	Core	c.7523G>A (p.Arg2508His)	AR	No
8	*RYR1*	MMC	c.3523G>A (p.Glu1175Lys) + c.11956dupG (p.Asp3986Glyfs*89)	AR	Yes
9	*RYR1*	TIP	c.3523G>A (p.Glu1175Lys) + c.10615delC (p.Arg3539Valfs*4)	AR	Yes
10	*MTM1*	CNM	c.1644+2T>C (p?) a splicing mutation	X-linked	No
11	*DNM2*	CNM	c.1124T>A (p. Val375Glu)	AD	No



(a &b). Electron microscopy (EM) of muscle biopsies of patients 4 & 5 with nemaline myopathy due to *KLHL40* mutation with roundish rods; (c&d). Electron microscopy of muscle biopsies of patient 2 & 3 with nemaline myopathy due to *ACTA1* mutation; (e) 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 1 with *ACTA1*-related congenital myopathy when the muscle biopsy was performed at 1.5 month old; (g & h) Muscle biopsy of patient 13 with multi-minicores on the EM; (i & j) Muscle biopsy of patient 8 with multi-minicore disease due to *RYR1* mutation showing uneven staining with SDH in some fibres and EM shows a large minicore 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).