found only in 2.25% of all muscle biopsies analyzed at Siriraj Hospital. DMRV is by far the most common distal myopathies in Thai population accounting for 50% of all cases and 80% of Thai DMRV patients carry GNE gene mutations. Dysferlinopathy is the second common distal myopathy in Thailand but only 25% of patients carry DYSF mutation. Many novel mutations of GNE and DYSF genes are identified.

doi:10.1016/j.nmd.2006.05.108

NUCLEAR ENVELOPATHIES; POSTER PRESENTATIONS

G.P.4.01

Rare congenital presentation of Emery-Dreifuss muscular dystrophy due to a novel de-novo LMNA mutation R249W

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We report an 8-year-old girl with congenital onset of Emery-Dreifuss muscular dystrophy (EDMD) with a novel LMNA gene mutation. The patient is the 2nd child born to non-consanguineous parents after a full-term uneventful pregnancy with normal intra-uterine growth. Mild ankle and knee contractures were present at birth. Her hypotonia did not come to medical attention until 4 months of age when persistent head lag was noted. Her head control worsened between 3 and 6 months of age. CK levels were 1050 and 1430. First neurologic evaluation at 8 months of age revealed generalized hypotonia and weakness with diminished reflexes. Genetic testing for SMA was normal. Muscle biopsy at 9 months showed only mild disparity in the size and shape of individual myofibers, normal immunohistochemistry stains and normal immunostaining for dystrophin, α-sarcoglycan and merosin. EMG at 2 years was essentially normal in distal lower limb but showed a lack of motor unit potentials without acute or chronic denervation signs in proximal upper extremity, paraspinal muscles and tibialis anterior. Brain MRI was normal. At 7 years of age the patient presented to our center for a repeat diagnostic evaluation. She had overall wasted appearance with almost no subcutaneous fat, in particular around her neck. There was no antigravity strength in the neck; no to minimal antigravity strength in proximal upper extremities; and barely present antigravity strength in proximal lower extremities. Multiple flexion contractures were present, including fingers, wrists, hips, knees and ankles. Spine showed mild scoliosis with rigidity. She has minimal facial weakness. Her cognitive skills were age appropriate. Her echocardiogram and Halter monitor studies have been normal. LMNA gene sequencing revealed R249W missense mutation that was not found in either of her parents. While R249W is a novel mutation, R249Q has been previously reported in multiple affected individuals with more classic EDMD. Mutations in the LMNA gene are known to cause a very broad phenotypic spectrum leading to nine distinct conditions. Congenital onset of EDMD is rare and has been reportedly only a few times. Given the lack of specific findings on muscle biopsy along with normal immunostaining results, this report further supports the need to consider LMNA gene mutations in merosin positive congenital muscular dystrophy cases with normal cognitive development.

doi:10.1016/j.nmd.2006.05.109

G.P.4.02

Pathophysiological mechanisms of lamin A/C associated Charcot-Marie-Tooth disease (CMT2B1/ARCMT2)

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Lamins, a class of intermediate filaments, are major components of the nuclear lamina, a filamentous network underlying the inner face of the nuclear membrane. A-type lamins are encoded by the same gene: LMNA, as a result of alternative splicing. Up to date, at least nine pathologies, described as laminopathies, have been associated with mutations in LMNA. One of these, Charcot-Marie-Tooth disease, type 2B1, is an autosomal recessive form of axonal hereditary motor and sensory peripheral neuropathy caused by the mutation c892C > T in exon 5 of the gene. In order to progress towards understanding the pathophysiological mechanisms underlying CMT2B1, we studied two different models for the disease: human patient's cells homozygous for the c892C > T mutation, and a murine Knock-In model. First, the role of LMNA in maintenance of nuclear integrity was assessed by immunofluorescent studies. Interestingly, no nuclear abnormalities were observed. Second, gene expression studies performed on microfluidic plates (Low Density Array) evidenced significant decreased expression levels for several genes, including LMNA. These observations were confirmed by Low Density Array experiments on brain, muscle and heart murine cDNA. Finally, in Knock-In models, behavioral, morphological and functional analyses are still in progress.

doi:10.1016/j.nmd.2006.05.110

G.P.4.03

Mutations in the lamin A/C gene: An emergent cause of fatal arrhythmias in congenital muscular dystrophies

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Mutations in lamins A and C, nuclear intermediate-filament proteins, cause a variety of diseases that primarily affect striated muscle, adipocytes, or peripheral nerves or cause features of premature aging. Muscle involvement is generally variable in severity, from congenital onset with severe phenotype to milder classic Emery-Dreifuss variant. There is no clear correlation between the clinical phenotype and type or localization of the mutations in proteins, which are generally amino acid substitutions or short deletions throughout the sequences. We report 2 patients (N2862, male and N4127, female) affected by congenital muscular dystrophy who developed cardiac arrhythmias due to a heterozygous de novo LMNA mutation. Both patients – born from non consanguineous marriages – presented with severe and diffuse hypotonia associated with delayed motor milestones, weakness, absent tendon reflexes, equinus and wrist contractures, very poor spontaneous activity, moderately increased serum CK levels. Mental development was normal as brain NMR. Muscle biopsy showed signs of mixed mus-

cle involvement and a normal staining for dystrophin, related glycoproteins and laminin alfa2. The evolution was relatively slow. Heart function – evaluated by standard and dynamic ecg and echo-color-dopplercardiography – was normal in patient N2862 until 8 years, when a 1st degree atrio-ventricular block was found in standard ecg. At the age of 9.5 years the patient experienced a sustained ventricular tachycardia requiring hospitalization and pharmacological treatment. He died one month later from sudden cardiac death. Conversely, in patient N4127 no overt sign of heart involvement was found except for a constant mild sinus tachycardia. At the age of 15 years she experienced an episode of atrial fibrillation converted in sinus rhythm by pharmacological treatment. DNA analysis revealed two novel heterozygous mutations in LMNA exon 1 (103-05delCTG, L35del) in patient N2862 and exon 4 (745 C > T, R249W) in patient N4127. Lamin A/C gene test should be included in the protocol of analysis of merosin-positive congenital muscular dystrophies to detect patients with a higher risk of arrhythmic events or cardiac sudden death.

doi:10.1016/j.nmd.2006.05.111

G.P.4.04

Lamin A/C gene mutation as a cause of dropped head syndrome. Extending the striated muscle laminopathies

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Dropped head syndrome is a common sight in several muscular disorders some of them associated with axial muscle involvement. However it can be a relevant feature in congenital muscular disorders in which lower limbs weakness is more preserved. We report two patients with this particular phenotype associated with a LMNA gene mutation. Two boys currently aged 4- and 3-year-old belonging to non consanguineous families were assessed at the clinical, radiological and muscle biopsy levels. LMNA gene was screened by DHPLC technique. The two patients presented in the first months weakness focused on their neck extensor muscle. They were never able to raise their head in decubitus prone position or control it in pull to sit manoeuvre. They sat down without support at 7 and 11 months with hyperlordosis and walked at 21 and 22 months old being totally unable to maintain their head in up right position. At last examination, both patients showed weakness and wasting in the upper limbs particularly in the scapular girdle while lower limb muscles were preserved with only mild Achilles tendon contractures and brisk deep tendon reflex. No muscle hypertrophy, facial dysmorphism and mental retardation were observed. CPK were up to 20 and 30 times normal values. Muscle biopsy revealed mild dystrophic features in the two patients. Cardiological evaluation and cranial MRI were normal. Genetic studies identified two new heterozygous LMNA gene mutations (c.1364G > C leading to R455P and c.1358G > C leading to R453P). Dropped head syndrome associated to muscular dystrophy in early infancy should remind us to look for a LMNA gene mutation.

doi:10.1016/j.nmd.2006.05.112

G.P.4.05

Phenotypic clustering of lamin A/C mutations in neuromuscular patients

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Mutations in the LMNA gene, encoding human lamin A/C, have been associated to an increasing number of disorders involving skeletal and cardiac muscle, peripheral nerve and more complex syndromic forms. We have screened a large cohort of patients for mutations in the LMNA gene. Our analysis identified 26 variants, eleven of which had not been previously described. By clustering LMNA mutated patients according to the age at onset of symptoms, we identified some interesting clinical and genetic correlations: (1) Patients with childhood onset displayed mainly neuromuscular disorder with scapuloperoneal distribution, while 63% of patients with onset in or after the third decade presented isolated cardiac dysfunction. These initial differences tended however to decrease with disease progression, as the coexistence of cardiac and skeletal muscle disorders was significant in both groups. Interestingly, the interval between the onset of neuromuscular and cardiac symptoms was correlated to the distribution of muscular weakness. (2) Most early onset patients were sporadic, whereas 75% of the adult-onset cases had a positive family history. (3) Frameshift LMNA mutations occurred almost exclusively in adult-onset patients with cardiopathy, while 93% of infantile cases carried in frame variations. In addition, the distribution of missense substitutions along the gene was different in the two groups. (4) Lamin A/C molecular structure analysis suggested that missense variations could alter either lamin filaments assembly at different levels or interactions with other ligands. These observations lead us to hypothesize that different pathogenetic mechanisms may determine the diverse disease phenotypes in the two groups. Moreover, our data sustain the necessity for a combined neurologic and cardiologic evaluation of patients as soon as LMNA defects are diagnosed, especially because the risk of sudden death due to malignant ventricular arrhythmias is high and symptoms may be underestimated.

doi:10.1016/j.nmd.2006.05.113

G.P.4.06

A new intermediate phenotype in a Swiss family with mutation in the LMNA gene

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We describe an overlapping phenotype of laminopathy in a Swiss family, and to point out the importance to screen for potential carriers as sudden death is frequent in mutations of lamin A/C encoding gene. Patients with laminopathy have various muscle and non-muscle tissue specific disorders, but all share cardiac abnormalities. Our family present an intermediate phenotype with rigid spine, limb girdle myopathy, elbow contractures and cardiomypopathy. Our index patient is a 37 yr