

the pathomechanisms underlying the findings in these two myopathies are most likely different.

doi:10.1016/j.nmd.2008.06.297

G.P.13.13

Identification and characterization of a novel congenital myopathy

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Congenital myopathies are a heterogeneous group of muscle diseases that classically present at birth with hypotonia, muscle weakness, and delayed developmental milestones. Over 40 types of congenital myopathies have been described, and are distinguished largely based on muscle biopsy findings. The pathomechanisms of some congenital myopathies are beginning to be understood, largely as a result of the elucidation of their genetic basis. However, many are not yet characterized in terms of their pathophysiology or genetic cause. We have identified a three generation family in which 5 members are affected with a novel form of congenital myopathy. This myopathy is clinically characterized by the onset of low muscle tone and weakness in infancy. Affected individuals stabilize during childhood but continue to exhibit mild weakness into adulthood. There is no involvement of facial or extraocular muscles. Histopathologic analysis on biopsy samples from three family members reveals unique changes, including an increase in Type I fibers, an abundance of centralized nuclei (>25% in one biopsy), and unusual cytoplasmic accumulations that are both desmin and actin immunoreactive. This combination of pathologic features has not been previously described. In an effort to identify the causative genetic alteration in this family, we performed linkage analysis using the Illumina HL12 SNP panel. We have excluded >99% of the genome, including genes and regions previously associated with congenital myopathies, and have identified 3 potentially linked chromosomal regions. These regions contain less than 100 genes. We are currently using a combination of candidate gene sequencing and comparative microarray gene expression analysis from muscle biopsy samples to uncover the genetic basis for this myopathy. In summary, we present pathologic and genetic evidence for a novel congenital myopathy.

doi:10.1016/j.nmd.2008.06.298

G.P.13.14

A new form of congenital myopathy with severe fibre immaturity

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We describe two boys of a non-consanguineous pedigree with a distinct myopathy characterized by fibre immaturity. Patient 1 displayed hypotonia and reduced spontaneous movements since birth. With clear disease progression, at one year of age, he had moderate facial weakness, conserved eye movements, weak cry, absent head control, froglike position of the legs, conserved antigravity movements of the forearms, but very poor hand and finger movements. Discrete contractures of elbow, hip

and knee joints were present. A progressive respiratory failure required assisted ventilation. He died at 15 months of age following a pulmonary infection. His uncle (patient 2) was less severely affected, learned to sit unsupported but did not acquire walking. At 14 years of age he has anti-gravity movements of the arms and does not require ventilatory support. Both patients had myopathic EMG findings and normal serum CK levels. Muscle biopsies at the age of one year revealed a striking reduction of the fibre size with almost no cytoplasm in several of the fibres. There was no evidence of fibre atrophy, degeneration or regeneration and no nuclear centralisation. Endomysial and septal connective tissue was increased. Proteins of the sarcolemma and basal lamina were normal. Fibre type distribution was normal and did not correlate to fibre size. An increased expression of neonatal myosin, trophin, vimentin, NCAM and desmin was observed. Electron microscopy showed a normal arrangement of contractile filaments. A biopsy of patient 2 at 14 years of age revealed a severe progression of muscle fibrosis, and only some sparse and extremely small fibres remained that were entirely immured by fibrosis. Remaining fibres were found in groups and adjacent mononuclear cells were found frequently. These two male patients seem to present a novel, likely X-linked form of congenital myopathy with an extreme fibre immaturity. The current workup includes to rule out a myotubular myopathy and to better characterise the mononuclear cells, which may represent myogenic precursors.

doi:10.1016/j.nmd.2008.06.299

G.P.13.15

Diagnosis and outcome of hypotonia in infancy

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Hypotonia in infancy can be the presentation of a wide range of neurological disorders. Despite extensive investigations, many infants remain undiagnosed. We describe our experience of investigation and diagnosis of hypotonic infants with a review of the survival rate at 1 year and identification other co-morbidities. A prospective, ethically approved, study of hypotonic infants referred to our tertiary neuromuscular clinic over a period of two years was carried out. Data was collected at both, at the initial, and 1 yr follow-up appointment noting perinatal history, age and severity of presentation, age and modality of diagnosis, survival at 1 yr and comorbidities. 19 infants were identified (12F:7M). Reduced fetal movements were noted in 8/19. 11 were floppy on Day 1 of life (range 4 days–4 months) and 5 had multiple contractures. 10/19 needed admission to a neonatal unit, 5 required invasive ventilation and 7 nasogastric feeds. CK was elevated (>2000 iu/l) in only 3/16 infants tested. A definitive diagnosis was reached by one year after presentation in only 11/19 infants with a combination of muscle biopsy, neuroimaging and genetic testing (1 spinal muscular atrophy, 1 Joubert's syndrome, 2 Prader-Willi syndrome, 3 merosin deficient congenital muscular dystrophy, 2 congenital myopathy, 1 Pompe's disease, 1 neuronal migration disorder). Fifteen infants were followed up at 1 yr of whom 3 died (1 SMA, 1 congenital myopathy, 1 undiagnosed). Motor development was delayed in all with persistence of head lag in 5/19. Three needed respiratory support (1 CPAP, 2 home oxygen) whereas 10 needed NG/gastrostomy feeds for growth faltering. Recurrent respiratory infections were common. Accurate diagnosis of hypotonic infants remains a challenge despite recent advances in neuroimaging, muscle immunocytochemistry and molecular genetics. 1-year survival in our study was 80%. Respiratory infections, feeding difficulties and growth faltering were significant co-morbidities. Prognosis remains dependent on final diagnosis.

doi:10.1016/j.nmd.2008.06.300