to run, jump or use stairs independently. At age 8 yr, her motor skills started to regress with emergence of weakness. She used a walker by 10 yr and lost ambulation at 12 yr. Currently, she cannot weight-bear (strength 1/5 in most leg muscles; quadriceps at 1-2/5), but has more preserved upper extremity use (strength 3 to 3-/5 range). She has hip, knee contractures, end-grade elbow contractures, and coexistence of finger flexor contractures with laxity in PIP and DIP joints. Her cognitive delays are typical for T21. She developed progressive scoliosis that required T4-L4 spinal fusion at 12 yr of age. There is no cardiomyopathy and her LVSF is 36%. Nocturnal hypoventilation started at age 13 yr with use of BiPAP during sleep since 16 yr of age. Unlike previously reported cases, she had a normal CK and her muscle biopsy at 14 yr did not show rimmed vacuoles or nemaline rods but rather severe myopathic changes: fibrosis and adipose infiltration, variation in fiber size with small, atrophic fibers intermixed with hypertrophic fibers, rounded and splitting fibers, increased central nuclei and occasional degenerating/regenerating fibers. To date, *ADSSL1* gene mutations, encoding an enzyme converting inosine monophosphate (IMP) to adenosine monophosphate (AMP), have been reported only in 9 Korean patients from 6 families with 8 of the 9 patients having the same compound heterozygous mutations, suggesting a founder-effect. Identification of another patient with novel mutations suggests that this form of myopathy is panethnic and likely underdiagnosed among patients presenting with signs of generalized and distal myopathy.

http://dx.doi.org/10.1016/j.nmd.2019.06.578

EP.121

Carey-Fineman-Ziter syndrome: a *MYMK*-related myopathy mimicking brainstem dysgenesis

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Carey-Fineman-Ziter syndrome (CFZS) is clinically defined by the combination of hypotonia, Moebius sequence, Robin sequence, facial anomalies, motor delay and growth failure. The etiology has remained elusive, although brainstem dysgenesis has been suggested. Recently CFZS was found to be associated with autosomal recessive mutations in the gene *MYMK*, which impair the fusion of mononuclear myoblasts to multinucleate myocytes in the skeletal muscle. We report a new case and define the clinical phenotype. The patient was the first boy from non-consanguineous parents. Pregnancy was unremarkable, but at birth he presented with hypotonia and bilateral facial palsy without external ophthalmoplegia. His facial appearance included small nose, retromicrognathia, downslanting palpebral fissures, low-set ears and a high arched palate. He also had feeding difficulties and needed nasogastric tube for a few months. There was generalized joint laxity and global muscular hypoplasia. During the first years of life his motor development was delayed; independent walking was acquired at age 2 and he used the Gowers' maneuver to come to an upright position. CK levels, nerve conduction study and electromyography were normal. Cranial MRI did not show any abnormalities, but a muscular MRI disclosed mild fatty infiltration of thigh adductors, gluteus and soleus muscles. Nevertheless, a muscle biopsy from quadriceps showed no myopathic features. Genetic testing by Whole-Exome-Sequencing detected two mutations in the *MYMK* gene: c.271C>A and c.399+5G>A. Nowadays he is 3.5 years old, he has no cognitive impairment and his motor abilities are improving slowly. CFZS is a congenital myopathy with prominent facial involvement, which is a diagnostic clue. There is variability in the pathology findings that may be explained by the muscle selected for biopsy or patient's age. Clinical course is static or slowly progressive, but the identification of new well characterized genetic cases will help to delineate the complete phenotype.

http://dx.doi.org/10.1016/j.nmd.2019.06.579

EP.122

Recurrent pneumothorax in an adult case of Ullrich congenital muscular dystrophy – case report and review of literature

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Collagen VI related muscular dystrophy is caused by dominant or recessive mutations in the *COL6A1*, *COL6A2* or *COL6A3* genes and comprises of a spectrum of rare neuromuscular disorders including the early-onset and more severe Ulrich congenital muscular dystrophy, the milder adult form of Bethlem myopathy and an intermediate phenotype. They are characterised clinically by progressive muscle weakness, distal hyperlaxity, joint contractures and respiratory insufficiency. Respiratory failure develops with progression of the condition and is caused by respiratory muscle (diaphragm and intercostal) weakness as well as spinal and thoracic deformities. Intrinsic lung disease is not common, but pneumothorax, occurring as a single event or as recurrent episodes is being increasingly recognised in these patients. Our patient is a 22 year old female with Ulrich congenital muscular dystrophy caused by heterozygous mutation in exon 9 of *COL6A1* gene. She was known to have a restrictive lung defect with scoliosis since childhood. Nocturnal ventilatory support was initiated at the age of 18 following a sleep study showing evidence of hypoventilation. She developed a spontaneous left sided pneumothorax at 21 years old, requiring intercostal drain (ICD) insertion followed by chemical pleurodesis via ICD. A contralateral spontaneous pneumothorax occurred 8 months later, which was complicated by PEA arrest requiring intubation and ventilation; followed by a protracted recovery period. This case is being presented to increase the awareness of a potentially life threatening complication associated with this condition. A first presentation of spontaneous pneumothorax in these patients should lead to careful assessment of lung parenchymal changes and consideration of definitive pre-emptive contralateral intervention.

http://dx.doi.org/10.1016/j.nmd.2019.06.580

EP.123

Selenoprotein-related congenital myopathy in two siblings

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Selenoprotein-related myopathy (SEPN1-RM) is a rare disease with a variable clinical presentation. Typically, patients have early onset respiratory insufficiency and relatively preserved limb muscle strength. Although the precise function of SEPN1 protein is uncertain, recent studies suggest a role in cell protection against oxidative stress. Prominent involvement of diaphragm muscle and skeletal muscle which are more vulnerable to oxidative stress probably may cause early respiratory involvement. Here we report two siblings with presenting early respiratory failure unrelated to limb weakness. 13 years-old girl was referred to hospital for weakness, coliosis, respiratory failure and growth retardation since 5 years. She was borned with uncomplicated delivery from consanguineous parents. Early neurodevelopment was normal. At 5 years old, she had been treated with growth hormone therapy because of short stature. Also, she was operated for scoliosis before 1 year from admission and used nocturnal noninvasive ventilator since then. On examination, she had myopathic face, scapular winging, muscle wasting, scoliosis, spinal rigidity and positive Gower's sign. Deep tendon reflexes were absent. Muscle strength was 3/5 in upper and 4/5 in lower extremities. SEPN1-RM was suspected based on a positive Gowers' sign, calf amyotrophy, limb-girdle dystrophy, rigid cervical spine and prominent and early nocturnal respiratory failure. A homozygous, known c.817G>A (p.Gly273Arg) mutation in the *SEPN1* gene was detected. Her 8 year old brother also examined because of frequent falls. He had mild axial hypotonia, generalised muscle atrophy, rigid cervical spine and facial weakness. He had also same mutation. Morning headaches, daytime fatigue and mild nighttime snoring raised suspicion of nocturnal hypercapnia.

After initiation of non-invasive ventilation, sleep quality improved and the headaches disappeared. Early respiratory failure in contrast to preserved skeletal muscle strength is a striking clue for this type of myopathy. Respiratory functions, especially in nighttime, should systematically and frequently be screened in all patients with SEPN1-RM. Early diagnosis is life-saving for patients to provide nocturnal noninvasive respiratory support.

http://dx.doi.org/10.1016/j.nmd.2019.06.581

EP.124

Myopathies presenting with head drop: clinical spectrum and treatment outcomes

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Dropped-head syndrome (DHS) can be the presenting feature of a wide spectrum of neurological conditions including a myopathy. There is a common presumption that myopathic DHS is frequently associated with a non-treatable, nonspecific myopathy. In this study, we performed a retrospective chart review to identify patients seen between 2000-2018, where head drop was the presenting or predominant feature of a myopathy, highlighting the clinical spectrum, extraskeletal muscle manifestations and treatment outcomes of myopathic DHS. We identified 107 patients with a median age at presentation of 68 years, and median duration of the head drop of 12 months. A specific diagnosis was reached in 53% of patients [inflammatory myopathy, 16 patients; myopathy with rimmed vacuoles, 10; radiation-induced myopathy, 8; sporadic late-onset nemaline myopathy, 7; myofibrillar myopathy, 4; facioscapulohumeral dystrophy, 3; inclusion body myositis 2; mitochondrial myopathy, 2; scleroderma-associated myopathy, 2; necrotizing autoimmune myopathy, 1; Binimetinib-induced myopathy, 1; and chronic lymphocytic leukemia-associated myopathy, 1]. Splenius capitis had the highest diagnostic yield for biopsy (67%). When tested, 89% of patients had abnormal pulmonary function tests, 50% abnormal swallow evaluation, 37% abnormal ECG and 13% abnormal transthoracic echocardiogram. 23 out of 43 (53%) treated patients responded to immunomodulatory therapy. Patient-reported limb weakness and neck flexion weakness on examination were associated with good response to treatment, while isolated neck extensor weakness was not associated with refractoriness to treatment. A wide spectrum of acquired and hereditary, treatable and non-treatable myopathies can present with DHS. Establishing a diagnosis is crucial for timely treatment administration, screening for extraskeletal muscle involvement, and counseling regarding prognosis

http://dx.doi.org/10.1016/j.nmd.2019.06.582

EP.125

***SCN4A* mutation causes episodic myotonia and persistent paralysis with internalized blood vessels in skeletal muscle**

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Mutations in the pore-forming subunit of the skeletal muscle sodium channel (*SCN4A*) have been generally considered as the original reason for hyperkalemic periodic, paramyotonia congenital and sodium myotonia. We reported a Chinese patient with unusual clinical and pathological features caused by mutation of *SCN4A*, p. I693T. This patient is a 25-year-old male who presented episodic flaccid paralysis at 7 years old. Paralytic attack may be triggered by rest after exercise, prolonged sitting and cold, lasting from several hours to 24 hours. Short term (several minutes) stiffness in eyelids, hands, and masticatory muscles could be induced by repetitive exercise and cold, which could be relieved by rest and warming-up. At 22 years of age, the patient experienced persistent weakness and daily transient stiffness in lower limbs. He was unable to climb stairs and stand up from the squatting position without assistance. When he was referred to our department again at 25 years old, he was wheelchair bound. Serum CK elevated ranging from 677U/L to 1274U/L. When the patient was placed on methazolamide and mexiletine respectively, the symptoms were obviously responsive to mexiletine rather than methazolamide. Apart from myotonic discharge observed on EMG examination at the first visit, myogenic changes with CRD discharge were also noted in recent examination, indicating a progressive damage of muscle fibers. Long exercise test showed CMAP decreased by 49%. Muscle MRI scanning revealed minor atrophy in bilateral thighs. Muscle biopsy of the left quadriceps femoris showed myopathic changes with splitting fibers and centrally placed nuclei in up to 80% of muscle fibers. Some vacuolated fibers and type I fiber predominance was observed. More importantly, about 40% of the muscle fibers, most of them are type 1 fibers, harbored internalized blood vessels. This is the first report of internalized blood vessels in numerous muscle fibers detected in muscle channelopathy caused by *SCN4A* mutation. The relationship between this unique pathological changes and clinical symptoms of myotonia and persistent muscle weakness is still unknown.

http://dx.doi.org/10.1016/j.nmd.2019.06.583

EP.126

Congenital fiber type disproportion related to novel autosomal dominant mutation in *TNNT1*

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Troponin T (TnT) is the tropomyosin binding subunit of troponin complex playing a central role in striated muscle contraction. Biallelic mutations in slow skeletal muscle TnT, encoded by *TNNT1*, have been reported to cause a rare form of nemaline myopathy (NM). The first TNNT1-NM has been associated to a single founder mutation in patients of Amish origin (ANM). Other three NM families have been reported later with different recessive loss-of-function mutations in *TNNT1*. Clinical phenotype in TNNT1-NM families is characterized by hypotonia, facial weakness, tremors (only in ANM), respiratory insufficiency and proximal weakness of varying severity. Recently, a heterozygous missense mutation in exon 9 of *TNNT1* was reported in a large family with autosomal dominant inheritance of NM, with considerable intrafamilial clinical heterogeneity and fiber type disproportion. We report an Italian 5 year old patient with severe neonatal hypotonia associated to orthopedic complications and delayed motor milestones. The girl, who is the only child of non-consanguineous parents, developed recently an infectious episode that progressed to severe respiratory failure needing respiratory support. Muscle biopsy showed congenital fiber size disproportion with a marked type I muscle atrophy and some undifferentiated type 2C fibers revealed by ATPase staining. Nemaline bodies were not observed. Next generation sequencing in this patient revealed a novel *de novo* heterozygous c.194A>C; p.(Asp65Ala) mutation in exon 8 of *TNNT1* affecting an high conserved residue in the Tropomyosin-Binding Site 1 of TnT. We describe the second *TNNT1*-related myopathy acting via a dominant mechanism and the first case without nemaline bodies in the muscle biopsy.

http://dx.doi.org/10.1016/j.nmd.2019.06.584
