CLINICAL RESPONSE OF NEUROMUSCULAR PATIENTS TO IVIG: AN INTERIM ANALYSIS OF THE INSIGHTS REGISTRY

T. Levine¹, J. Katz², R. Barohn³, T. Mozaffar⁴, G. Wolfe⁵, D. Saperstein¹, L. Katzin⁶, M. Dimachkie³, E. Ritt⁷, L. Vaughan⁷, M. Greer⁷ (¹Phoenix Neurological Associates; ²California Pacific Medical Center; ³University of Kansas; ⁴University of California, Irvine; ⁵University at Buffalo; ⁶University of South Florida; ⁷NuFACTOR Specialty Pharmacy)

Introduction: Despite established criteria for diagnosis, there is variability in patients prescribed intravenous immunoglobulin (IVIG) in neuromuscular practice.

Objectives: To determine clinical criteria predictive of a positive response in patients prescribed IVIG.

Methods: Data was collected from over 400 IVIG patients. A panel of independent neuromuscular neurologists reviewed information provided to payers to obtain approval for IVIG. Outcomes were determined by quality-of-life measures, Patient-Global-Impression-of-Change (PGIC), and clinical documentation.

Results: The largest group of patients who began IVIG were diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) (N=105). Of these, 36% were felt by reviewers to have objective improvement by month three. This corresponded to 40% improvement in PGIC. Statistical analysis is underway to evaluate which factors were predictive of response.

Conclusions: IVIG response rates in CIDP patients are below 40%. This project suggests variability in diagnosis and IVIG dosing may affect this rate. Identifying predictive factors of response may improve the cost-effectiveness of IVIG for CIDP.

PROPOSED MECHANISM FOR POST-EXERCISE WEAKNESS IN HYPOKALEMIC PERIODIC PARALYSIS

Wentao Mi*, Fenfen Wu**, and Stephen Cannon** (¹Department of Neurology & Neurotherapeutics, UT Southwestern Medical Center, Dallas, TX; **Department of Physiology, DGSOM at UCLA, Los Angeles, CA)

Severe attacks of weakness often occur within minutes of rest after strenuous exercise in HypoKPP. While this is a cardinal feature of the disorder and the molecular defect is known, the mechanism is completely unknown. We tested the hypothesis that acidosis is a trigger for exercise-induced attacks. In our mouse models for HypoKPP (CaV1.1-R528H and NaV1.4-R669H), acidosis is well tolerated (pH 6.8 in 25% CO₂) but upon return to normal pH of 7.4 (5% CO₂) the maximal tetanic force for the soleus transiently decreased by more than 50% for 20 minutes. The transient weakness did not occur for WT muscle. A model is proposed wherein acidosis promotes a shift of chloride into muscle to produce sustained depolarization and weakness in HypoKPP, but not WT, muscle. Supported by NIAMS of the NIH.

IS THE RITUXIMAB RESPONSE IN ACETYLCHOLINE RECEPTOR AUTOANTIBODY MYASTHENIA GRAVIS DURABLE?


Introduction: Rituximab has demonstrated benefit in patients with myasthenia gravis (MG) who are refractory or have intolerable side effects to current therapy.

Objective: Assess the durability of rituximab response in patients with acetylcholine receptor autoantibody (AChR+) MG.

Design/Methods: This is a retrospective study of 16 refractory AChR+ MG patients. Immunoetherapy regimens and examinations before and after treatment were reviewed. Number of rituximab cycles, duration since last treatment cycle, response to treatment and durability of response was collected.

Results: Clinical improvement was observed in parallel to withdrawal of other immunotherapies in eleven of sixteen patients (69% complete responders). The remaining five patients showed clinical benefit but have been unable to completely withdraw other immunotherapies. Nine patients (56%) have relapsed in an average of 36 months (range 29-44).

Conclusion: B-cell depletion therapy affects a durable response for 24-75 months in approximately 2/3 of patients, with approximately 1/2 relapsing ~3 years after treatment.

STRATIFIED COHORTS AND NATURAL HISTORY STUDIES AT THE MRC CENTRE FOR NEUROMUSCULAR
DISEASES – A TOOL TO TRANSLATE DISCOVERY SCIENCE INTO TREATMENTS FOR PATIENTS


Introduction: One of the aims of the MRC Centre is to translate research findings into clinical trials and new treatments for patients with neuromuscular diseases (NMDs).

Objectives: To deep phenotype patients with NMDs, to define valid and responsive outcome measures and to validate robust disease biomarkers.

Methods: Patient recruitment and stratification at the clinical, genetic, histopathological, electrophysiological, serologic and imaging level. Sample collection and storage of biomaterials.

Results: Our stratified cohorts are rapidly expanding. We had 12 stratified cohorts ongoing by February 2013 and 23 cohorts by 2015. We had 2896 patients enrolled in stratified cohorts by 2013 and 6310 patients enrolled by 2015.

Conclusions: The MRC Centre patient cohorts whose core diagnostic and phenotypic data are being aligned to stored biomaterials and accurate contemporary natural history studies are crucial to deliver translational medicine. Such cohorts are the basis for proof of principle studies of potential therapies and clinical trials.

ABSTRACT PRESENTATION- DAY 2

MRI PATTERN IN THE WORKUP OF DISTAL MYOPATHIES


Introduction: Distal myopathies are a diagnostically challenging group with more than 15 causative genes described.

Objectives: To determine diagnostic workup of distal myopathy patients and examine whether muscle MRI patterns advance the diagnostic process.

Methods: We reviewed records of all patients attending the muscle clinic with probable or confirmed distal myopathy. The pattern of lower limb MRI muscle involvement was compared with that in the literature and scored as typical, consistent or different for each genotype. A neurologist used clinic-pathological features to independently categorize possible genetic diagnoses.

Results: 38 patients with distal myopathy were identified. Fifteen were genetically confirmed, 5 were initially misdiagnosed as IBM, 11 required repeated muscle biopsy. Compared with clinico-pathological classification, MRI pattern generated a smaller number of genetic hypotheses (mean 1.4 ± 1.4 vs 8.8 ± 3.3); avoided misdiagnosis (IBM hypothesis 0% vs 28%) and identified those with myotilin mutations.

Conclusions: Systematic MRI pattern analysis may improve the diagnostic process.

SQSTM1 AND VCP MUTATIONS IN A SERIES OF 205 INCLUSION BODY MYOSITIS CASES

Q. Gang1, C. Bettencourt1*, S. Brady1,2, J. L. Holton1, A. M. Pittman1, D. Hughes1, E. Healy1, M. Parton1, D. Hilton-Jones2, P. B. Shieh3, M. Needham4, C. Liang5, E. Zanottelii, L. Valente de Camargo6, B. De Paepe7, J. De Bleecker7, A. Shaibani8, M. Ricolone9, M. Moggio9, R. J. Barohn10, M. M. Dimackie10, M. Mora9, R. Manetegazza9, S. Zanotti9, A. B. Singleton11, M. G. Hanna1, H. Houlden1, P. M. Machado1*, The Muscle Study Group and The International IBM Genetics Consortium (London, UK1; Oxford, UK2; Los Angeles, California3; Perth, Australia4; New South Wales, Australia5; Sao Paulo, Brazil6; Ghent, Belgium7; Houston, Texas8; Milan, Italy9; Kansas City, KS10; Bethesda, Maryland11)

*Equally contributed to the work.

Introduction: Clinico-pathologically overlapping inherited disorders indicate that genetic factors might be involved in sporadic inclusion body myositis (IBM) pathogenesis.

Objectives: To identify genetic risk factors associated with IBM.

Methods: Whole-exome sequencing was performed in 205 IBM patients. Muscle tissue was pathologically evaluated and whole-transcriptome expression profiles generated.

Results: We identified eight rare missense mutations in the SQSTM1 and VCP genes in 10 IBM patients (5%). Five of the mutations had been previously reported in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) with Paget’s disease of bone (PDB); p62 staining was increased and MHC-I was up-regulated in the muscle tissue of these patients.

Conclusions: Variants in SQSTM1 and VCP may constitute genetic susceptibility factors for IBM. The occurrence of mutations in SQSTM1 and VCP in IBM, ALS, FTD and PDB reinforces the link between these disorders, pinpointing converging pathogenic pathways resulting in impaired autophagy-lysosome processing, causing dysregulation of protein homeostasis.
TOLL-LIKE RECEPTOR ANTAGONISM AS A NOVEL ANTI-INFLAMMATORY THERAPEUTIC APPROACH FOR DUCHENNE MUSCULAR DYSTROPHY

Jessica Boehler¹, Kanneboyina Nagaraju¹, Mark Hurtt², Sudhir Agrawal² (¹Center for Genetic Medicine Research, Children’s National Medical Center, Washington, DC; ²Idera Pharmaceuticals, Cambridge, MA)

Introduction: Immunologically triggered inflammatory processes play a central role in the pathogenesis of Duchenne muscular dystrophy (DMD). Toll-like receptors (TLRs) are key components of the innate immune system. IMO-8400 is a novel oligonucleotide antagonist of TLRs 7, 8 and 9 that demonstrated anti-inflammatory activity in patients with autoimmune disease.

Objective and Methods: To characterize in vivo activity of a novel TLR antagonist in a DMD model, we conducted studies in mdx mice. Across studies, treated mice received one of several TLR antagonist regimens for 5 weeks and were assessed on multiple measures.

Results: Treatment resulted in significant reductions in inflammation, serum creatine kinase, and gene expression of IL-6. An increase in the specific force of isolated extensor digitorum longus muscle was also observed.

Conclusions: Data from preclinical studies in mdx mice support advancing the TLR antagonist drug candidate IMO-8400 into clinical development as a potential non-steroidal anti-inflammatory treatment for DMD.

WHOLE EXOME SEQUENCING OF SPORADIC IBM PATIENTS IDENTIFIES NOVEL RISK ALLELES

C.C. Weihl and M.B. Harms (Department of Neurology, Washington University School of Medicine, Saint Louis, MO)

Introduction: While candidate genetic studies in sIBM have been performed there have been no studies utilizing large scale unbiased genetic approaches.

Objective: Identify novel genetic risk factors and therapeutic targets in sIBM.

Methods: We performed exome sequencing on 65 sIBM patients. All patients had muscle biopsy material and fulfilled, at least, ENMC 2013 criteria for probable sIBM. Exome datasets were filtered for rare coding variants and compared with 615 existing control patient exomes.

Results: 20% of sIBM patients carried rare DYSF variants (including two previously reported pathogenic variants) compared with 6.6% of controls (p=0.024) and 7.6% of sIBM patients vs 0.07% of controls (p=0.0051) carried a single [c.2143C>G; p.R715G] missense variant in the myosin chaperone UNC45B.

Conclusions: These studies suggest that sIBM patients may carry genetic variants that increase the risk or severity of sIBM. These variants may point to potential therapeutic targets aimed at treating sIBM.

OUTCOME MEASURES

A COMPARISON OF SIX-MINUTE WALK TEST PERFORMANCE BETWEEN CHILDREN WITH CONGENITAL MYOTONIC DSTROPHY (CDM) AND HEALTHY CONTROLS

E. Pucillo*, H. Hayes*, D. DiBella*, N. Johnson*, R. Butterfield*, M. Hung*, W. Chen*, B. Crockett*, M. Dixon*, J. Bounsanga*, C. Campbell** (Department of Neurology, University of Utah, Salt Lake City, UT; Children’s Health Research Institute, London, Ontario, CA**)

Introduction: CDM is one of the most common muscular dystrophies affecting physical function. Differences between children with CDM and age-matched healthy controls (HC) in six-minute walk test (6MWT) distance have not been documented.

Objectives: Determine if 6MWT distance differs between subjects with CDM and HC, and also in comparison to their age/gender/height predicted values.

Methods: 36 (21 CDM, 15 HC; 3-14 years) performed 6MWT (meters) and predicted values were calculated using the Geiger et al equation.

Results: Mean (SD) distance for subjects with CDM was 304.8 (119.8) m, and mean (SD) distance for age-matched HC was 577.3 (SD 65.57) m, and difference between the two groups (p < 0.05). Children with CDM differed from 18-76% (males) and 19-90% (females) of their Geiger equation 6MWT predicted normal values.

Conclusion: Children with CDM show a significant difference in 6MWT distance when compared to Geiger equation predicted values and their age-matched HC.

A POSITIVE MCMANIS TEST IN A SERIES OF PATIENTS WITH MUSCLE DISEASE BUT WITHOUT PERIODIC PARALYSIS

Introduction: The McManis test (long exercise test) is a sensitive and specific electrophysiological test used in the diagnosis of periodic paralysis (PP).

Objectives: To investigate patients with muscle disease who have a ‘false-positive’ McManis test.

Methods: Clinical, histopathological and molecular genetic data were collected on 8 patients with muscle symptoms but without typical features of periodic paralysis who had an abnormal McManis test.

Results: The clinical and histopathological features were variable between patients and did not concur with PP phenotypes described in the literature. Some patients had mitochondrial abnormalities on muscle biopsy but no mitochondrial genetic changes and in two patients RYR1 mutations were found.

Conclusion: Patients with an abnormal McManis test in this series represent a heterogeneous group with a range of clinical and histopathological features.

Accurate Slice Selection Improves Responsiveness of Quantitative Lower Limb Muscle MRI in CMT1A Patients


Background: Treatment trials for neuromuscular diseases require responsive outcome measures. We aim to improve responsiveness (standardised response mean [SRM]=mean change/SD of change) of calf 3-point Dixon fat quantification in CMT1A, by comparing analysis methods.

Methods: 14 CMT1A/8 controls underwent baseline/12 month right calf MRI, measuring muscle fat fraction (ff) across 10 slices, each 2cm apart. SRM was compared for different methods of analysis in terms of slice selection: (a) central slice; (b) closest slice to mid calf; weighted average of (c) 2, (d) 4 and (e) 6 slices centred at mid calf.

Results: In CMT1A, mean ff increased significantly in all muscles by all methods excepting (a). Highest SRM in more sophisticated methods. For EHL, SRM: 0.71;0.83;1.00;1.11 for methods b;c;d and e.

Conclusion: Accurate analysis with respect to slice localisation is critical to maximising MRI outcome measure responsiveness; translating to fewer participants needed in clinical trials adequately powered to detect treatment efficacy.

Feasibility and Reliability of the 2 Minute Walk Test and 6 Minute Walk Test in Children with Congenital Myotonic Dystrophy


Introduction: Feasibility and reliability of the 6 minute walk test (6MWT) have not been assessed in children with congenital myotonic dystrophy (CDM). The 6MWT may not be as feasible as a 2 minute walk test (2MWT) due to poor concentration and fatigue in children with CDM.

Objectives: This study examined the feasibility, reliability and correlation of the 2MWT and 6MWT for children with CDM.

Methods: 24 children with CDM (3-14 years) attempted the 6MWT on consecutive days. The first 2 minutes of the 6MWT was measured and referred to as the 2MWT.

Results: 100% of the children were able to complete the 2MWT and 87.5% completed the 6MWT. The 2MWT and 6MWT results correlated ($r = 0.94$) and both were reliable (6MWT ICC = 0.91; 2MWT ICC = 0.83).

Conclusions: The 2MWT correlates with the 6MWT and is more feasible in children with CDM.

Feasibility of Assessing Muscle Strength and Physiological Fatigue in Adults with Myotonic Dystrophy, Preliminary Results

M. Pautler, H. Hayes, C. Trujillo, D. DiBella, E. Pucillo, M. Dixon, R. Butterfield, N. Johnson (University of Utah, Salt Lake City UT)

Introduction: Individuals with Myotonic Dystrophy Type 1 (DM1) have muscle weakness and fatigue contributing to increased falls and decreased quality of life (QOL). Assessment of physiological fatigue has not been widely studied in DM1.

Objective: Determine feasibility of assessing physiological fatigue through maximum voluntary isometric contraction (MVIC) and fatigue index (FI) in individuals with DM1.

Methods: Quantitative muscle analysis (MVIC, max force(kg) of 3-second contraction; FI, % change of 30-second sustained max contraction) was assessed on bilateral hand grip, ankle dorsiflexion, and knee extension.
**Results:** Nine subjects (5 males, 4 females, mean age 35). Grip: MVIC 14(6), FI 24%; Ankle dorsiflexion: 7(3)kg; FI 28%; Knee extension: 22(6)kg; FI 11%.

**Conclusions:** It is feasible to determine physiological fatigue in DM1. Dorsiflexion and grip strength demonstrated 25% strength decline with sustained contraction. To determine the role of fatigue in falls and QOL, further quantitative assessment of muscle strength and fatigue is warranted.

---

**14**

**PATIENT REPORTED QUALITY OF LIFE IN CONGENITAL MUSCULAR DYSTROPHY: RESULTS OF QUALITATIVE INTERVIEWS**

K. Cornwall, N.E. Johnson, R.J. Butterfield

**Introduction:** Congenital muscular dystrophies (CMD) cause a spectrum of weakness and cognitive impairment. Research is limited in exploring health related quality-of-life (HRQOL) in CMD.

**Objectives:** Our goal is to explore the HRQOL in CMD, specifically Ullrich CMD (UCMD) and Bethlem Myopathy (BM).

**Methods:** We conducted interviews with parents of children with UCMD/BM or patients if older than age 8. Participants represented a wide range of ages and degree of disability. Interviews focused on identifying issues impacting patient HRQOL. Interviews were recorded, transcribed, coded, and analyzed using a qualitative framework technique.

**Results:** We interviewed 14 UCMD/BM patient-parent dyads. Difficulties with mobility and ambulation were among the most frequently cited themes, though issues with mental and emotional domains were frequently cited.

**Conclusions:** Patient interviews regarding HRQOL in CMD provide a comprehensive understanding of symptoms and disease course associated with CMD, allowing the development of HRQOL instrument for use in future clinical trials.

---

**15**

**RELIABILITY AND VALIDITY OF THE 6-MINUTE WALK TEST AS AN OUTCOME MEASURE IN OCULOPHARYNGEAL MUSCULAR DYSTROPHY**

S. Youssof, M. Fernandez* (Albuquerque, NM, Tucson, AZ*)

**Introduction:** Oculopharyngeal muscular dystrophy (OPMD) causes ptosis, dysphagia, and limb weakness. Validated outcome measures for use in clinical trials have not been established. The 6-minute walk test (6MWT) is a widely used measure in other neuromuscular diseases.

**Objective:** We investigated the reliability and validity of the 6MWT in OPMD.

**Methods:** 26 individuals with OPMD and 20 controls completed a battery of strength, functional, and patient-reported assessments. Test-retest reliability was determined using intraclass correlation coefficients, known groups validity was determined using t-tests, and convergent validity was determined using Pearson’s correlation coefficients.

**Results:** The 6MWT had excellent test-retest reliability and correlated strongly with manual muscle testing ($r=0.79$, $p=0.0000$) and with the PROMIS physical function short form ($r=0.77$, $p=0.0000$). Mean 6MWT was lower in OPMD subjects vs. controls ($387.4 \pm 82.8$ vs. $463.4 \pm 73.2$, $p=0.0023$).

**Conclusion:** The 6MWT is a reliable and valid outcome measure in OPMD. Responsiveness over time should be investigated in a longitudinal study.

---

**16**

**RESPONSIVENESS OF THE MYASTHENIA GRAVIS IMPAIRMENT INDEX (MGII)**

Barnett C, MD, PhD(c)1,2; Vera B, MD, FRCP1; Kapral M, MD2,3; Kulkarni A, MD, PhD2,4; Davis AM, PhD2,5,6 (1Division of Neurology - Department of Medicine. University of Toronto and University Health Network. Toronto, Canada; 2Institute of Health Policy, Management and Evaluation. University of Toronto, Canada; 3Department of Medicine. University of Toronto and University Health Network. Toronto, Canada; 4Department of Neurosurgery. Sick Kids Hospital. Toronto, Canada; 5Division of Health Care and Outcomes, Toronto Western Research Institute, University Health Network; 6Department of Physical Therapy and Graduate Department of Rehabilitation Science, University of Toronto, Toronto, Canada)

**Background:** The Myasthenia Gravis Impairment Index (MGII) is a new measure of myasthenia gravis severity at the impairment level.

**Objectives:** To assess the responsiveness of the MGII.

**Methods:** Patients receiving IVIG, plasmapheresis (PLEX) or prednisone were assessed at baseline and after treatment, with the MGII and other measures. Patients from reliability studies were used as controls. We analyzed between and within-group change and the responsiveness efficiency of the different measures. Meaningful change was assessed through the patient impression of change (PIC).

**Results:** Treated patients had significantly higher change in scores than controls. The effect size and standardized response mean were higher for IVIG/PLEX than prednisone. The MGII had higher relative efficiency than other measures tested. MGII change scores were significantly different by PIC categories.
Conclusions: The MGII is responsive with different treatments. The MGII can detect statistical and patient meaningful change and has higher responsiveness efficiency than other measures tested.

EVALUATION OF NATIONAL SPECIALIST SERVICE FOR MITOCHONDRIAL DISEASES

N. James, E. Bugiardini, S. Holmes, M.G. Hanna (London, UK)

Introduction: The National Specialist Service for Mitochondrial Diseases was established in April 2007 to improve management of patients with mitochondrial diseases.

Objective: To evaluate our service in terms of clinical activity and patient’s experience.

Methods: We reviewed all patients attending our service from September 2012 to June 2015 evaluating the number of new patients, follow-up, who did not attend (DNA) and genetically confirmed/unconfirmed (GC/GU). Patient experience survey started in July 2015.

Results: 177 new (2.8% DNA) and 506 follow-up patients (12% DNA) were seen. The evaluation included a physiotherapist and a nurse specialist assessment. 31% of the new referrals were already genetically confirmed. Of the 71 GU who have a follow-up 28% have received a genetic diagnosis. Patient experience survey is ongoing.

Conclusions: The service manages a high number of patients providing a multidisciplinary assessment and a fast diagnostic pathway. Patient survey could show how to further improve our service.

CLINICAL MANAGEMENT

IN-DEPTH ANALYSIS OF NEUROLOGIC COMPLICATIONS OF ANCA VASCULITIS IN A LARGE INCEPTION COHORT REVEALS NOVEL ASSOCIATIONS

1Anahit Mehrabyan, MD; 2JulieAnne G. McGregor, MD; 2Caroline J. Poulton, MSW; 2Yichun Hu, MS; 2Patrick Nachman, MD; 2Ronald J. Falk, MD; 2Susan L. Hogan, PhD; 2William F. Pendergraft III, MD; 1Chafic Y. Karam, MD (1Department of Neurology, UNC, Chapel Hill, NC; 2Kidney Center, UNC, Chapel Hill, NC)

Objectives: To characterize neurologic complications in patients with ANCA associated vasculitis (AAV).

Methods: Patients from the Glomerular Disease Collaborative Network (GDCN) AAV inception cohort diagnosed from 1970-2012 were evaluated for neurologic complications.

Results: Of 658 patients, 56 (8.5%) had central nervous system (CNS) (n=9) or peripheral nervous system (PNS) (n=48) complications related to ANCA vasculitis. Of the 9 with CNS dysfunction, 5 had seizures, 3 had CNS vasculitis with altered mental status, and 1 had vasculitic myelitis. Of the 48 patients with PNS complications, 8 had cranial nerve lesions, 2 had myopathic disorders and 38 had peripheral neuropathies. When compared to patients without neurologic involvement, those with neurological complications were different with respect to ANCA specificity and kidney involvement and function.

Conclusions: PNS complications are more frequent than CNS in AAV. Patients with neurologic involvement are less likely to have MPO ANCA and kidney involvement.

LONGITUDINAL FOLLOW UP OF MEDICAL COMORBIDITIES, NEURODEVELOPMENT AND HEALTH RELATED QUALITY OF LIFE IN CONGENITAL MYOTONIC DYSTROPHY

C. Nguyen, M. Prasad, R. Hicks, M. MacKay, C. Campbell (London Health Sciences Centre, London ON)

Introduction: Congenital Myotonic Dystrophy (CDM) is an autosomal dominant multisystemic disorder caused by a triplet repeat expansion in the DMPK gene.

Objectives: To describe the medical morbidity, developmental profile, and health related quality of life (QOL) in a CDM cohort.

Methods: Prospective cohort study of CDM patients identified via the Canadian Pediatric Surveillance Program from 2005-10. Symptomatology and QOL were assessed through semi-annual medical reports and questionnaires.

Results: Seventeen CDM patients (8 males: 9 females), were followed from diagnosis for several years (3-7 years follow up). Repeat size ranged from 700-2600. The most frequently encountered complications in infancy were feeding and respiratory difficulties. Developmental milestones were delayed. Over time the physical and psychosocial QOL scores remained relatively stable in this cohort.

Conclusions: The use of data from this active surveillance, prospective cohort of CDM patients allows a better understanding of the comorbidities, developmental and QOL natural history in early childhood.

MORTALITY IN A COHORT OF MITOCHONDRIAL PATIENTS

I. Skorupinska, A. Horga, M.G. Hanna, E. Bugiardini (London, UK)
**Introduction**: Several studies have evaluated prognostic factors for specific mitochondrial diseases. However, few studies have specifically evaluated the cause of death and contributing factors.

**Objectives**: To identify the cause of death of patients attending a mitochondrial specialist clinic.

**Methods**: We reviewed records of all patients attending the mitochondrial clinic that deceased in the last 25 years. Patients were screened if classified as having a mitochondrial disease based on the muscle biopsy results or genetic sequencing.

**Results**: We retrieved death certificates of 23 patients with mitochondrial disease. The mean age of death was 48.04 ± 17.63 (SD), the range was 20-83. The main causes of death were cardiac (39%) and respiratory (26%). Two patients had an unexpected cardiac death: an m.3243A>G patient with only hearing loss and a patient with SANDO.

**Conclusions**: Cardiac disease was the leading cause of death in our cohort of mitochondrial patients irrespective of the phenotype.

---

**OCCURRENCE OF ANTI-HU AND LAMBERT-EATON MYASTHENIC SYNDROMES IN A PATIENT WITH SMALL CELL LUNG CANCER**

Anahit Mehrabyan, MD, Chafic Karam, MD, Nizar Chahin, MD (UNC, Department of Neurology)

**Objectives**: To report the unusual occurrence of Anti-Hu antibody and Lambert-Eaton Myasthenic syndrome (LEMS) in a patient with small cell lung cancer (SCLC).

**Case report**: A 40 year-old female admitted to the psychiatry eating disorders unit for management of persistent nausea. Within a month after the admission she developed pneumonia and mediastinal lymphadenopathy necessitating intubation. At the same time she developed ileus, burning and tingling in legs and left hand, severe diffuse weakness. Nerve conduction studies and EMG revealed a severe, length dependent, axonal, sensory-motor polyneuropathy and presynaptic neuromuscular junction disorder. The paraneoplastic (PNP) panel was positive for anti-Hu antibodies and Voltage Gated Calcium channel antibodies (VGCC). The biopsy of mediastinal nodes was consistent with SCLC.

**Conclusion**: Severe persistent ileus can be the initial presentation of anti-Hu syndrome, as well as LEMS. Association of ileus with severe sensory-motor neuropathy and mediastinal lymphadenopathy should highly suggest SCLC associated with PNP syndrome.

---

**RE-EVALUATING THE GOLD STANDARD OF DIAGNOSIS FOR POMPE DISEASE**

A. Genge, N. Campbell (Montreal, Quebec, Canada)

**Introduction**: Previous reports suggest that although a diagnostic muscle biopsy can confirm the presence of Pompe disease, the absence of a definitive biopsy result does not rule out the diagnosis.

**Objectives**: We attempted to determine the how many cases were not diagnosable on the biopsy alone.

**Methods**: We reviewed patients with a limb girdle syndrome who demonstrated nonspecific abnormalities of muscle, without evidence of the classical changes of acid maltase deficiency. These patients were re-screened for Pompe disease using dried blood spot (DBS) testing.

**Results**: Twenty-seven patients provided blood samples for the DBS test. Five patients underwent subsequent genetic testing. Genetic analysis demonstrated that one patient tested positive for Pompe disease, and one patient had one copy of a pathogenic variant.

**Conclusions**: The ability of a diagnostic muscle biopsy to definitively rule out the presence of Pompe disease is limited. There is a role for DBS testing in patients presenting with a limb girdle syndrome.

---

**THE RELATIONSHIP BETWEEN BONE MINERAL DENSITY AND CARDIOVASCULAR FUNCTION IN DUCHENNE MUSCULAR DYSTROPHY**

TA Kervin, M Thangarajh (Washington, D.C.)

**Introduction**: Secondary osteoporosis is common in DMD. Epidemiological studies suggest that there is an inverse relationship between poor bone mineral density (BMD) and cardiovascular health outcomes.

**Objective**: Whether there exists an independent association between low BMD and development of cardiac dysfunction in boys with DMD is presently unknown.

**Methods**: Retrospective BMD data and left ventricular ejection fraction (LVEF) were obtained from DMD patients. A simple linear regression was performed to assess the relationship between BMD and LVEF. Multivariate logistic regression models were used to assess the relationship between BMD and incidence of left ventricular dysfunction, and significant decline in LVEF.

**Results**: The association between BMD and decline in LVEF will be reported. Whether low BMD increased the odds of having left ventricular dysfunction will be determined.

**Conclusion**: This study will determine whether low BMD is a new additional risk factor for the development of poor cardiac outcomes in muscular dystrophy.

---

**RETROSPECTIVE REVIEW OF HOSPITALIZATIONS OF MYOTONIC DYSTROPHY ADMISSIONS AND**

MUSCLE & NERVE September 2015 S7
COMPLICATIONS AT COLUMBIA UNIVERSITY MEDICAL CENTER

S Teed, (JB Sampson)

Introduction: The myotonic dystrophies (DM) are multisystemic disorders that may result in hospitalization and increased complication risk.

Objectives: Perform a retrospective chart review of DM inpatient admission diagnoses and complications.

Methods: A retrospective chart review (01/01/1987-09/16/2014) of 60 inpatient visits from 26 DM patients was performed, with matched controls for common admission diagnoses.

Results: Erroneous coding of ICD9 359.21 was found in 35/100 cases.

Females accounted for 73.3% of admissions. Admissions clustered in the youngest and oldest age ranges. Top admission diagnoses were: pneumonia, gastrointestinal problems, cardiac problems, impaired mental status and scoliosis.

Urinary complications occurred more frequently in DM patients than in controls ($z = .022$, Mann-Whitney U test).

Conclusions: The gender discrepancy may be due to scoliosis, pneumonia and cardiac symptoms being more common in women. Admissions in children were largely scoliosis related. Urinary complications in DM patients could be due to greater illness severity, Foley catheterization duration, or immune susceptibility.

SURVEY OF PREGNANCY IN PATIENTS WITH CHARCOT-MARIE-TOOTH DISEASE AND RELATED HEREDITARY NEUROPATHIES

M. Skorupinska*, M. Laurá*, K. Bull*, B. Byrne**, M. G. Hanna*, M. M. Reilly* (*MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London UK; **Coombe Women and Infants University Hospital, Dublin)

Introduction: CMT is the most common inherited neuropathy. Patients frequently ask whether pregnancy will affect their CMT, whether CMT will affect their pregnancy, the optimal delivery type and whether they/their child may have a higher risk of complications. Few studies address these questions.

Objectives: We assess the impact of pregnancy on CMT, and that of CMT on pregnancy, delivery and care of the newborn.

Methods: We designed a questionnaire divided into four parts (prior, during/after pregnancy and delivery), including 29 questions addressing impairment, falls, pain, fatigue and respiratory complications during these periods; delivery type, complications, anaesthetic details and difficulties looking after the newborn.

Results: Preliminary results show deterioration of CMT symptoms during pregnancy in most women (6/10) with resolution after delivery in all but two. There were no anaesthetic complications.

Conclusion: Data from this survey provides valuable information on current practice and will inform future guidelines/standards of care in CMT.

CLINICAL TRIALS

ANTICIPATING AND OVERCOMING OBSTACLES IN SETTING UP NIH FUNDED ACADEMIC LED, INTERNATIONAL CLINICAL TRIALS IN RARE DISEASE - LEARNING FROM FOR DMD

R. Davis¹, M. Guglieri¹, K. Hart², E. McColl¹, B. Herr, W. Martens², J. Wilkinson¹, M. Eagle¹, W. King², M. Brawn², M. McDermott², R. Tawil², D. Hirtz³, J. Kirschner³, K. Bushby¹, R.C. Griggs² (¹Newcastle University, Newcastle upon Tyne – UK; ²University of Rochester School of Medicine and Dentistry, Rochester, NY, USA; ³National Institute of Neurological Disorders and Stroke, NIH, USA; ⁴University of Freiburg, Freiburg, Germany)

FOR DMD is an academic led clinical trial in Duchenne Muscular Dystrophy. The trial was funded by NIH for 5 years (July 2010 to June 2015), anticipating that all sites (40 across USA, Canada, UK, Germany and Italy) would be open to recruitment from July 2011. However, study start-up was significantly delayed and recruitment did not start until January 2013.

The time from first contact to site activation across countries ranged from 6 months to 24 months. Reasons of delay were both global (drug procurement, budgetary constraints) and country specific (complexity and diversity of regulatory processes, contracting).

The push for new treatments in rare disease is being hindered by several factors, being the divergent landscape of international clinical trial regulations one of them. Based on the FOR DMD experience, we have devised a checklist of steps to anticipate and minimize delays in academic international trial initiation but also identify obstacles that will require a concerted effort on the part of many stakeholders to mitigate.

DESIGN OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 clinical trial of THE TOLL-LIKE RECEPTOR ANTAGONIST IMO-8400 IN PATIENTS WITH DERMATOMYOSITIS

MUSCLE & NERVE September 2015
Introduction: Dermatomyositis (DM), a severe idiopathic inflammatory myopathy, is characterized by chronic autoimmunity in muscle and skin. Toll-like receptors (TLRs) are key components of the innate immune system involved in the disease pathogenesis. IMO-8400 is a novel oligonucleotide antagonist of TLRs 7, 8 and 9 that has demonstrated activity in patients with psoriasis.

Objectives: We designed a Phase 2 clinical trial of IMO-8400 in DM patients to evaluate safety and tolerability, change in skin disease activity, and change in muscle strength and function.

Methods: Key study entry criteria include adults with definite or probable DM aged 18-75 years; Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score ≥15; clinical symptoms of active muscle disease and abnormal serum CK or ALD, EMG, muscle biopsy or MRI. Patients will be randomized 1:1:1:1 to one of three IMO-8400 treatment arms or placebo (N=12 each), and treated by subcutaneous injection for 24 weeks.

EPISODIC ATAXIA TYPE 1: NATURAL HISTORY, QUALITY OF LIFE AND PATIENT-REPORTED SYMPTOMS

T. D. Graves 1 MRCP, PhD, R. C. Griggs 2 MD, B. N. Bundy 3 PhD, J. C. Jen 3 MD, PhD, R. W. Baloh 4 MD & M. G. Hanna 1 MD, on behalf of the CINCH investigators (1MRC Centre for Neuromuscular Disease, UCL Institute of Neurology, Queen Square, London. WC1N 3BG. UK; 2Department of Neurology, University of Rochester School of Medicine & Dentistry, Rochester, NY 14642. USA; 3Paediatrics Epidemiology Centre, University of South Florida College of Medicine, Tampa, FL 33612. USA; 4Department of Neurology, UCLA Medical School, Los Angeles, CA 90095-1769. USA)

Introduction: Episodic ataxia type 1 is due to potassium channel, KCNA1 mutations. No prospective studies have been performed.

Objective: Obtain quantitative data on progression and provide a baseline for clinical trials.

Methods: Multicenter, longitudinal natural history study. Recruitment September 2006 to March 2010 with three annual visits. Outcome measures were: standardized symptom interview, SARA score, Short Form-36 quality of life measure and standardised assessment of Activities of Daily Living. Automated interactive telephone-based voice response diary recorded symptoms, frequency/severity of attacks for 8 weeks following annual visits.

Results: 33 patients were enrolled: 23 had one year follow up and 19 two years. SARA, activities of daily living scale, SF-36 and IVR will be presented. Very little progression was noted over two years, suggesting that any future drug trial would show benefit during this timescale.

Conclusions: We provide the first documentation of the natural history of this disorder.

Supported by: DHHS/PHS/NIH grant 2U54NS059065-07.

RECRUITMENT IN THE FOR-DMD STUDY - DOUBLE-BLIND RANDOMIZED TRIAL TO OPTIMIZE STEROID REGIME IN DUCHENNE MUSCULAR DYSTROPHY (DMD)

M. Guglieri 1, K. Hart 2, E. McColl 1, B. Herr, W. Martens 2, J. Wilkinson 1, M. Eagle 1, W. King 2, M. Brawn 2, M. McDermott 2, Rabi Tawil 2, Deborah Hirtz 3, J. Kirschner 4, R.C. Griggs 2, K. Bushby 1 (1Newcastle University, Newcastle upon Tyne – UK; 2University of Rochester School of Medicine and Dentistry, Rochester, NY, USA; 3National Institute of Neurological Disorders and Stroke, NIH, USA; 4University of Freiburg, Freiburg, Germany)

The FOR DMD study is an international multi-centre study aiming to enrol 300 boys. The study opened to recruitment in January 2013. Up to July 2015, the study screened 182 subjects and enrolled 149 subjects across 36 sites in 5 countries. Study set up has been a long process with extended delay in site activation. Patient enrolment rate has been slower than anticipated. Recruitment rates ranged from 0 to 1.72 subjects per open site per month. Average rate of recruitment to date is 0.16 per open site per month with some differences among countries (US: 0.16; Canada: 0.16; UK: 0.22; Italy: 0.10; Germany: 011). Possible factors affecting recruitment include: reliance on outdated recruitment projections in site selection, time from ethics approval to first recruit, engagement of site Principal Investigator and other study staff at the site, provision of dedicated study staff and engagement of the national patient community. Awareness of factors that impede recruitment could improve study conduct in other trials.

PATHOGENESIS

ADAPTIVE IMMUNE RESPONSE TO THERAPY IN HMGCR AUTOANTIBODY MYOPATHY
Introduction: The cellular immunology of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)-autoantibody myopathy is unknown.

Objectives: To evaluate B and T cell responses to immunosuppression in a case of HMGCR-autoantibody myopathy.

Methods: We performed lymphocyte phenotyping prior to and every 4 months after immunosuppressive therapy. Among T cell subsets, we assessed CD45RA-CXCR5 T follicular helper (Tfh) cells as well as the capacity of CD4 and CD8 T cells to produce IFN-γ, TNF-α, IL-17, IL-4, and IL-2 following stimulation.

Results: Baseline HMGCR autoantibodies were 201 units and CK was 21,539. Immune profiling demonstrated a strong Th1 response and strikingly elevated Tfh cell and plasmablast frequencies. We did not detect Th2 or Th17 anomalies. After 1 year of therapy, CK was 3,890, autoantibodies were 80 units, and manual muscle testing normalized. Tfh cells and plasmablasts also normalized.

Conclusions: High Tfh cells and plasmablasts are associated with HMGCR-autoantibody myopathy and may represent therapeutic biomarkers.

NEW INSIGHTS INTO B CELL AND T CELL CONTRIBUTIONS TO MYASTHENIA GRAVIS IMMUNE DYSREGULATION

Yonghao Cao1*, Jae-Yun Lee1*, Panos Stathopoulos1, Sasha Gupta1, Robert A. Amezquita2, Steven H. Kleinste1, Jonathan M. Goldstein1, Richard J. Barohn3, Mazen M. Dimachkie3, Richard J. Nowak1 and Kevin C. O’Connor1† (1Department of Neurology, Yale School of Medicine, New Haven, CT, USA; 2Department of Pathology, Yale School of Medicine, New Haven, CT, USA; 3Department of Neurology, University of Kansas Medical Center, Kansas City, MO, USA)

*Equal contribution. †Senior & Presenting Author

Objective: Determine whether the autoimmune mechanisms contributing to myasthenia gravis (MG) include compromised B-cell tolerance and antigen-specific Th17 cells.

Background: Tolerance defects, which have been unexplored in MG, allow accumulation of selfreactive B-cells, which may then feed populations producing pathogenic autoantibodies. The antigen-reactive T-cell compartment contributes to MG autoimmunity by providing essential B-cell help, however the phenotype of these cells requires refinement.

Methods: Validated assays to measure the frequency of self-reactive naive B cells accumulate in MG. MG-derived T-cell libraries proliferate in response to AChR-associated antigens and produce IFN-γ, IL-17 and GM-CSF but not IL-10.

Conclusion: MG includes B-cell tolerance checkpoint defects and autoreactive T-cells that display a program consistent with a pro-inflammatory, pathogenic Th17 phenotype. These newly described mechanistic components of MG autoimmunity are of particular importance when considering the durability of MG treatment modalities.

NOVEL HISTOPATHOLOGICAL FEATURES IN A PATIENT WITH A NOVEL MUTATION IN DNAJB6 GENE (LGMD 1D LOCUS)

Stanley Iyadurai, MSc PhD MD, Jennifer Roggenbuck, MSc, and Miriam Freimer, MD

Introduction: Mutations in DNAJB6 gene cause LGMD 1D. Three missense mutations (involving amino acids 277 and 279) in DNAJB6 have been described. These patients have childhood-onset or adult-onset lower-extremity predominant proximal or proximal-and-distal weakness, and muscle biopsy shows endomysial fibrosis, angulated and rounded fibers, rimmed vacuoles and abnormal accumulations of SMI-31, TDP-43 and DNAJB6 aggregates.

Case Report: We describe a patient with childhood-onset, lower extremity-predominant proximal weakness associated with foot drop, and elevated CK (3 times the upper limit of normal). EMG/NCS showed a proximal, irritable myopathy.

Results: A next-generation myopathy panel revealed a novel mutation in DNAJB6, resulting in P286L change. Muscle biopsy revealed multiple internal nuclei, ring fibers, angulated and rounded fibers and rimmed vacuoles.

Conclusions: To our knowledge, this is the first report of multiple internal nuclei and ring fibers in patients with LGMD 1D. This case extends the genotypic and phenotypic spectrum of LGMD 1D.

NOVEL MUTATION IN CACNA1S EXTENDS THE PHENOTYPIC SPECTRUM OF PERIODIC PARALYSIS PHENOTYPES: ELECTRODIAGNOSTIC AND HISTOPATHOLOGICAL FEATURES

Stanley Iyadurai, MSc PhD MD, Jennifer Roggenbuck, MSc, and John Kissel, MD

Introduction: CACNA1S mutations presenting with hypokalemic periodic paralysis phenotype reside in the “sensor” domains of the transmembrane segments of the CACNA1S.
**Case Report:** We report the case of a 47-year old man with a 25-year history of episodic weakness of legs, aches, cramps, diffuse pain, exertional dyspnea and elevated CK. No specific episodes of total paralysis or hypokalemia were reported. Neurological examination showed proximal weakness in the lower extremities, knee flexion- and finger abduction- weakness, distal sensory loss, normal reflexes and down going toes.

**Results:** EMG/NCS revealed an irritable, proximal myopathy. Long exercise test was positive. Muscle biopsy showed inflammatory infiltrates, multiple internal nuclei and clear vacuoles. A next-generation myopathy panel revealed a novel mutation in CACNA1S (corresponding to T1009M change in the non-sensor transmembrane domain).

**Conclusions:** We propose that the non-sensor domain mutations may manifest in an atypical fashion with pain/lethargy and accompanied fixed weakness.

**PHARMACOKINETICS AND PHARMACODYNAMICS OF THE SELECTIVE FAST SKELETAL MUSCLE TROPONIN ACTIVATOR, CK-2127107**

J. Andrews, V. Vijayakumar, J. James, J. Lee, S. Kulke, A. Bian, L. Meng, F. Malik, A. Wolff (Cytokinetics, Inc., South San Francisco, CA (in collaboration with Astellas Pharma Inc.))

**Introduction:** CK-2127107 slows calcium release from fast skeletal muscle troponin, sensitizing the sarcomere to calcium and increasing skeletal muscle contractility, which may enhance physical performance in patients with neuromuscular diseases.

**Methods:** The safety, pharmacokinetics and pharmacodynamics of CK-2127107 were evaluated in three randomized, placebo-controlled studies in healthy subjects.

**Results:** Single and repeated dosing was well tolerated. No differences in PK between younger and older subjects emerged. During transcutaneous stimulation, tibialis anterior muscle force increased with the dose and plasma concentration of CK-2127107 at every time point tested after dosing and was most evident at the mid-range of stimulation frequencies.

**Conclusions:** Single doses and multiple doses of CK-2127107 to steady state appeared well-tolerated, and amplified the response of muscle to nerve activation in healthy volunteers. These data support the progression of CK-2127107 into Phase 2 clinical trials in patients with spinal muscular atrophy.

**T CELL REACTIVITY IN INCLUSION BODY MYOSITIS (IBM)**


**Introduction:** The reactivity of cytotoxic CD8+ T-cells in IBM remains uncertain.

**Objectives:** To phenotype and characterize the function of peripheral T-cells from IBM patients.

**Methods:** We phenotyped CD4+/CD8+ T-cell subsets in 9 healthy controls and 15 patients with IBM. We also examined intracellular staining for Th1, Th2, Th17, and Tfh cell cytokines after stimulation.

**Results:** We identified no significant Th2 (IL-4), Tfh (CD4+CD45RA-CXCR5+) or Th17 (IL-17) pathology. Naive T-cells were decreased in IBM patients and the majority of cytokine-producing CD8+ T-cells were CD45RA+CCR7- terminal effectors (p<0.01). We observed significantly higher percentages of IFN-γ, TNF-α, and IL-2 producing CD8+ T-cells (p<0.001). Polyfunctional T-cells producing multiple inflammatory cytokines were also significantly increased. Similar results were observed in CD4+ T-cells.

**Conclusions:** CD8+ T-cells in IBM mediate a strong response driven by highly over-reactive terminal effector cells producing Th1-associated pro-inflammatory cytokines. Other inflammatory mechanisms, such as Th17 and Tfh pathways, appear to be less important.

**NETWORK**

**CANADIAN NEUROMUSCULAR DISEASES NETWORK (CAN-NMD) A COLLABORATIVE APPROACH FOR ESTABLISHING WORLD CLASS OUTCOMES FOR NEUROMUSCULAR DISEASES IN CANADA**


**Introduction:** Canada has a very collegial neuromuscular disease (NM) community and the CAN-NMD will further enhance NM clinical care, research and education capabilities and promote collaboration between NM stakeholders nation-wide.

**Objectives:** Funded in 2014, the CAN-NMD aims to facilitate improved outcomes for NM patients in Canada through enhanced clinical care, and enriched research capability and education.
**Methods:** The CAN-NMD features several task forces, each devoted to a specific aim of the Network’s activities, devised in October 2014 by a group of NM clinicians, scientists and other stakeholders.

**Results:** In the area of clinical care, the CAN-NMD will focus on creating pathways; building community; and striving for excellence. In research, the CAN-NMD will work on creating roadmaps; enhancing collaboration; and assuring quality.

**Conclusion:** The creation of the CAN-NMD represents a significant step forward to improve the consistency of clinical care, the quality of research and education for all NMs across Canada.

---

**PREVALENCE STUDY OF MUSCLE CHANNELOPATHIES IN ITALY**

Maggi L⁴, Lo Monaco² M, Portaro S³, G. Meola⁴, JF Desaphy⁵, Lucchiari S⁶, Pagliarani S⁶, Ulzi G⁶, Bernasconi P¹, R Brugnoni¹, P Imbricki⁷, G Comi¹, R Mantegazza¹, F Gerardi⁷, M Trojano⁵, D’Amico A⁶, Pegoraro E⁹, Politano L¹⁰, Mongini T¹¹, Vercelli L¹¹, Siciliano G¹², Ricci G¹², Conte-Camerino D⁵, A Toscano² and VA Sansone⁷ on behalf of the Italian Network for Muscle Channelopathies (¹Neuromuscular Diseases and Neuroimmunology Unit, Foundation Neurological Institute C Besta, Milan; ²Neurophysiology Unit, Cattolica University, Rome; ³Department of Neurosciences, University of Messina; ⁴IRCCS Policlinico San Donato, University of Milan; ⁵Dept. Pharmacology, University of Bari; ⁶Dino Ferrari Centre Department of Pathophysiology and Transplantation Neuroscience Section (DEPT) University of Milan, Neurology Unit Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; ⁷Centro Clinico NEMO Milan, Neurorehabilitation Unit, University of Milan; ⁸Unit of Neuromuscular and Neurodegenerative Disorders, IRCCS Bambin Gesù Children’s Hospital, Rome; ⁹Department of Neurosciences, University of Padua; ¹⁰Cardiovascular and Medical Genetics, Second Naple’s University; ¹¹Department of Neuroscience, University of Turin; ¹²Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa)

**Background:** Hereditary skeletal muscle channelopathies (SMC) are rare diseases whose prevalence in Italy is yet unclear.

**Objective:** To define the prevalence rate of SMC in Italy and the frequency and distribution of associated mutations.

**Methods:** We reviewed clinical, laboratory, and genetic SMC data from 3 Italian neuromuscular laboratories.

**Results:** Of 620 genetically confirmed SMC, 526 are non-dystrophic myotonias (73% CLCN1 and 27% SCN4A), 34 hyperkalemic periodic paralysis (SCN4A), 45 hypokalemic periodic paralysis (CACNA1S and SCN4A) and 15 Andersen-Tawil syndrome (KCNJ2). All SCN4A (except an unreported 9-nucleotide deletion) and 70.7% of CLCN1 mutations are missense. Most CACNA1S and KCNJ2 mutations are common mutations.

**Conclusions:** Prevalence of SMC in Italy is similar to that in other countries. We confirm clinical and genetic heterogeneity with a limited number of mutations accounting for a large number of cases. This information will help for the search of a personalized therapy through functional and pharmacological studies of mutations.