News Science Anthology

Highlighting journal articles of interest in the areas of NM and EDX medicine.

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A Comparison Between IVIg and Plasma Exchange as Preparations Before Thymectomy in Myasthenia Gravis Patients
Utility of Paraneoplastic Antibody Testing in the Diagnosis of Motor Neuron Disease


This is a retrospective chart review of 138 patients with motor neuron disease (MND) who had paraneoplastic antibody testing using the Mayo Clinic paraneoplastic antibody panel. Of these patients, 101 were ultimately diagnosed with ALS (possible, probable or definite according to El Escorial criteria) and 27 were diagnosed with suspected ALS or another form of MND. Of all patients tested, 9% (13/138) were positive for at least one antibody. The antibodies found were VGCC (4 patients), striated muscle (4 patients), VGKC (3 patients), GAD-65 (3 patients), ganglionic AchR (2 patients). Malignancy screening was performed on 9 of these 13 patients, and was negative in all cases. All 13 of these patients developed progressive deficits and were ultimately diagnosed with ALS.

Comment: Extensive investigations for explanations other than MND are often performed at first consideration of the diagnosis. Unfortunately, an etiology other than MND is rarely uncovered. Confirmed paraneoplastic motor neuron disease appears to be a rare entity and was not identified in any of the patients in this retrospective study. Paraneoplastic antibodies did not affect prognosis. Though paraneoplastic antibodies are useful in well-characterized neuromuscular syndromes (e.g. myasthenia gravis, Lambert-Eaton myasthenic syndrome), they are of limited value in typical MND.

C9orf72 Ablation in Mice Does Not Cause Motor Neuron Degeneration or Motor Deficits


The hexanucleotide expansion in the C9orf72 gene is the most common genetic cause of amyotrophic lateral sclerosis (ALS), but basic questions about its pathogenicity are unanswered. Koppers and colleagues investigated the possibility that loss-of-function mutations are responsible for the clinical phenotype by generating a conditional C9orf72 knockout mouse. This knockout mouse did not demonstrate motor neuron degeneration, motor deficits, or reduced survival compared to wild-type mice. The authors conclude, therefore, that C9orf72 loss-of-function by itself is not sufficient to cause motor neuron disease.

Comment: The function of C9orf72 is not known. Previous works supports the role of C9orf72 haploinsufficiency in ALS: C9orf72 mRNA and protein expression is reduced in brain tissue of patients with ALS, and motor deficits developed in C9orf72 knockout models in zebrafish and C. elegans. The results of this study question the role of C9orf72 haploinsufficiency in patients with ALS, though the authors do acknowledge that loss-of-function may have a regulatory role important to disease pathogenesis. Further investigation of the contribution of C9orf72 mutations to the development of ALS will hopefully offer greater insight into disease pathogenesis and possibly identification of attractive therapeutic targets.
Targeting the Colony Stimulating Factor I Receptor Alleviates Two Forms of Charcot-Marie-Tooth Disease in Mice


Charcot-Marie-Tooth (CMT) disease is a heterogeneous group of inherited neuropathies. Although CMT is due to mutations in Schwann cell-related genes, a secondary role for inflammation in disease pathophysiology has been identified. Klein and colleagues examined the role of inhibition of the macrophage colony stimulating factor 1 receptor (CSF1R) using the kinase PLX5622. In studies of CMT due to connexin-32 mutations (Cx32def) and P0 deletions (P0het), treatment with PLX5622 reduced macrophage numbers and typical histopathological abnormalities. In addition, compound muscle action potential (CMAP) amplitudes and muscle strength were increased in treated mice, with greater benefit reported for the Cx32def mice than the P0het mice.

**Comment:** Despite identification of more than 80 gene mutations responsible for the CMT phenotype, no curative treatments have been identified. Whether the histopathological, electrophysiological, and clinical improvements that occur with PLX5622 are due to reduced axon destruction, increased sprouting, or another mechanism is not yet known. Nevertheless, the results of this study suggest that CSF1R antagonists are a promising treatment, and that they should be explored further.

Recurrence of Pain After Usual Nonoperative Care for Symptomatic Lumbar Disk Herniation: Analysis of Data From the Spine Patient Outcomes Research Trial


The Spine Patient Outcomes Research Trial (SPORT) is a large multi-center randomized trial with a concurrent observational cohort study involving 13 spine centers in 11 US states. This article examines the prevalence of back and leg pain recurrence in the subset of 478 patients receiving conservative care for lumbar disc herniation. The type of conservative care was not uniform and could include education, medications, therapy, epidural steroid injections, or other interventions. Back or leg pain was assessed on a 7-point scale of sciatica bothersomeness for up to 4 years of follow-up. Of the 478 patients, 217 experienced initial resolution of pain (defined as bothersomeness score <2). Recurrence of back pain (defined as bothersomeness score >2) was 28% at one year and 70% at three years. Recurrence of leg pain was 23% at one year and 51% at three years. History of smoking and comorbid joint pathology were related to higher rates of recurrence. Posterolateral disc hernination and complete leg pain resolution were related with decreased rates of recurrence.

**Comment:** The SPORT trial is notable for being the largest study of its kind, and the AANEM NSEB has previously presented updates on findings related to surgical management of spinal stenosis. There is scant epidemiological data on the rate of pain recurrence following conservative management of lumbar disc herniation, and these study results provide practical information which the clinician can use to counsel patients on the likelihood of recurrent pain.
**Fludarabine in the Treatment of Refractory Chronic Inflammatory Demyelinating Neuropathies**


Chronic inflammatory demyelinating polyneuropathy (CIDP) is treated most commonly with oral steroids and intravenous immunoglobulin. Options for patients with refractory disease include plasmapheresis, cyclophosphamide, azathioprine, mycophenylate mofetil, and rituximab. Up to one third of patients with CIDP have a poor response to treatment, particularly patients with anti-MAG antibodies. Fludarabine is a nucleoside analog antimetabolite which incorporates into DNA and induces apoptosis. It predominately affects B1 lymphocytes and has been shown to be helpful in IgM-related CIDP. This article describes a case series of 8 patients with CIDP treated with fludarabine at a dose of 25mg/m² per day for 5 days every 5-8 weeks. Improvement was noted in all 8 patients. Fludarabine was generally well tolerated but two patients had hematologic side effects necessitating treatment discontinuation.

**Comment:** Corticosteroids and intravenous immunoglobulin are effective in only 60-70% of patients with CIDP. Fludarabine has shown efficacy in the treatment of CIDP associated with monoclonal gammopathy and distal acquired demyelinating symmetric neuropathy, and may be an option for patients with refractory disease.

**Does Electrodiagnostic Confirmation of Radiculopathy Predict Pain Reduction after Transforaminal Epidural Steroid Injection?**


This paper describes an observational cohort study of 170 patients undergoing transforaminal epidural steroid injection for cervical or lumbar radiculopathy, who had previously undergone EMG within the prior 6 months. The relationship between EMG diagnosis and pain improvement following epidural steroid injection was evaluated. At follow-up >30 days post injection, a larger proportion of patients with EMG-confirmed radiculopathy (37.7%) described >50% relief of symptoms as compared to patients with negative EMG (17.8%). This association was significant for lumbar, but not cervical radiculopathy.

**Comment:** Prior studies have reported mixed conclusions about the benefit of epidural steroid injections for lumbar radiculopathy, and no previous studies have reported data on EMG as a predictor of response to epidural steroid injections. Previous studies have been limited by small size and diverse procedural interventions. It is important to note that the response to epidural steroid injections for relief of radiculopathy pain was low in this study, likely related to the fact that EMGs were most often ordered to clarify the presence of radiculopathy in patients with atypical presentations.

Epidural steroid injections can provide meaningful improvements in pain and function for individuals with radiculopathy. Determining which patients may benefit most from these interventions, possibly using EMG as an adjunct to clinical information, will help determine the most effective treatment strategies and help contain growing healthcare expenditures.
Use of Clinical and Electric Myotonia to Differentiate Childhood Myopathies

In this study, the aim was to evaluate how the presence and the pattern of myotonic discharges found on EMG could help with the diagnosis of muscle disease in children. Electrical findings would be used with clinical findings, including family history. This study resulted in the development of an algorithm with the startpoint being electrical myotonia. Ghosh and Sorenson identified 20 EMGs from 2030 pediatric EMGs performed between April 2004 and March 2014 at the Mayo Clinic Rochester. This retrospective chart review further subdivided patients into those with clinical myotonia (9 patients) and those with without clinical myotonia (11 patients). Patients in the second subgroup did not have clinical myotonia by history or by exam (absence of percussion or induced myotonia). The 9 patients in the clinical myotonia group did not have clinical weakness, elevated CK levels, or fibrillation potentials. These patients had abundant myotonic discharges that were seen in 100% of the muscles tested. These patients were ultimately were diagnosed with myotonia congenital (8 patients) or paramyotonia congenital (1 patient). The diagnosis was either confirmed by genetic testing (CLCN1 mutation or SCNA4 mutation) or by clinical findings and family history. In the second group, the patients were weak or hypotonic. Just over half had elevated CK levels. The myotonic discharges in this group were seen in patches (12.5-67% of muscles tested) and were of short duration. This group had a more variable set of associated ultimate diagnoses: congenital myopathy (3 patients), muscular dystrophy (3 patients), inflammatory myopathy (4 patients), and congenital muscular dystrophy (1 patient).

Comment: The algorithm resulting from this study is helpful in diagnosing neuromuscular disease associated with myotonia. As pointed out by the authors, the limitations include that this study was based on the EMG records. Patients that were diagnosed by clinical history and findings then later confirmed by genetic testing may not have been included as they may not have had an EMG.

Oral Steroids for Acute Radiculopathy Due to a Herniated Lumbar Disk – A Randomized Clinical Trial

This randomized, double-blind, placebo-controlled clinical enrolled 269 adults with radicular pain below knee for 3 months or less and MRI evidence of herniated intervertebral disk. Participants were randomized in a 2:1 ratio to receive a 15-day course of oral prednisone (5 days each of 60 mg, 40 mg, and 20 mg) or matching placebo. Outcome measures included Oswestry Disability Index (ODI), change in lower extremity pain, SF-36, Physical Component Summary (PCS), Mental Component Summary (MCS), and spine surgery rate at 3 weeks and 1 year. Greater improvement was noted in ODI scores at 3 weeks and at 1 year in prednisone-treated compared to placebo-treated patients. Pain reduction at 3 weeks and 1 year also favored the prednisone group, but was much less robust. There were no differences in the surgery rates at 1 year follow up. Adverse events, none major, were more common in the prednisone group compared to the placebo group (49.2% vs 23.9%).

Comment: Acute lumbar radiculopathy due to intervertebral disk herniation is a common disorder that causes substantial pain and disability. Though spontaneous recovery occurs in most patients, epidural steroid injections and lumbar discectomy are commonly performed in patients with a chronic relapsing remitting course or in those who do not respond to conservative treatment. Despite conflicting evidence, ESI is performed frequently. Over the past 35 years, six trials have evaluated the use of non-epidural steroid in patients with sciatica and most of these studies did not find evidence of efficacy of the steroid treatment. In this trial, the authors found a small, statistically significant improvement in function at both 3 weeks and at 1 year. The use of prednisone did not decrease the likelihood of undergoing surgery and did not lead to significant pain improvement.
A retrospective review of 223 patients diagnosed with ocular myasthenia gravis at two academic medical centers between 1986 and 2013 was conducted. All patients underwent serum testing for the acetylcholine receptor (AChR) binding antibody using alpha-bungarotoxin; values greater than 0.02 nmol/L were considered positive. AChR antibody testing was positive in 70.9%. Generalized myasthenia gravis developed in 20.2% of patients during the follow-up interval of 60 months. The mean antibody level in patients who developed generalized symptoms (12.7 nmol/L) was significantly higher than in those who did not develop generalized symptoms (4.2 nmol/L) \((P = .002)\).

**Comment:** Myasthenia gravis causes weakness of the eyelids and extraocular muscles in 90% of patients, and approximately half of such patients will present with isolated ocular symptoms. The AChR antibody test is highly specific but historically has shown a sensitivity of less than 50%. The antibody was elevated in 70% of patients in this study. Possible explanations for the higher sensitivity identified in this study include improved testing methods, longstanding disease, careful exclusion of mimics of ocular myasthenia gravis, and lengthy follow-up periods.
Taouroursodeoxycholic Acid in the Treatment of Patients With Amyotrophic Lateral Sclerosis

Taouroursodeoxycholic acid (TUDCA) is a hepatically-synthesized hydrophilic bile acid used for treatment of chronic cholestatic liver diseases. Experimental studies suggest that TUDCA may have cytoprotective and anti-apoptotic effects, with potential neuroprotective activity.

In this pilot study, 34 ALS patients were randomized to receive either TUDCA (1 g twice daily for 54 weeks) or placebo after a lead-in period of 3 months. The primary outcome measure was the proportion of patients with improvement of at least 15% in the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) slope during the treatment period as compared to the lead-in phase. Secondary outcomes included between-treatment comparison of ALSFRS-R at study end, comparison of the linear regression slopes for ALSFRS-R mean scores, and the occurrence of adverse events.

The treatment group showed a higher proportion of responders compared to those who received placebo (87% vs. 43%, p = 0.021). At study end baseline-adjusted ALSFRS-R was significantly higher (P = 0.007) in TUDCA than in placebo groups. Comparison of the slopes of regression analysis showed slower progression in the TUDCA than in the placebo group (P < 0.01). TUDCA was well tolerated; there were no between group differences in adverse events.

Comment: This pilot study provides preliminary clinical data indicating that Taouroursodeoxycholic acid (TUDCA) is safe and may be effective in slowing the progression of ALS.

Ocular Vestibular Evoked Myogenic Potentials as a Test for Myasthenia Gravis

Valko and colleagues describe the use of ocular vestibular evoked myogenic potentials (oVEMP) in patients with myasthenia gravis. The technique is based on the vestibulo-ocular reflex, and involves application of a repetitive vibratory stimulus to the skull with a mini shaker and recording of evoked responses from the inferior oblique muscles using facial electrodes. Thirteen patients with isolated ocular myasthenia gravis and 14 with generalized myasthenia gravis were studied, and compared to 28 healthy controls. All of the patients with generalized myasthenia gravis had ocular symptoms and 7 of the 27 myasthenics were seronegative for both acetylcholine receptor and MuSK antibodies. oVEMP using a unilateral decrement of 15.2% or greater produced a sensitivity of 89% and a specificity of 64% for myasthenia gravis, while a bilateral decrement of 20.4% or greater produced a 100% sensitivity, but a sensitivity of only 63%.

Comment: oVEMP may be a useful test for evaluation of patients with myasthenia gravis. It offers two potential advantages compared to currently available techniques. First, the extraocular muscles are directly accessible, which is not true of any currently used technique. Second, the sensitivity for ocular myasthenia gravis may be greater than antibody assays, single fiber electromyography, or repetitive nerve stimulation. Further refinement of the technique in larger groups of subjects (with particular attention to defining cutoffs for normal and abnormal) and application of oVEMP in a prospective fashion are necessary before it is applied widely.
Long-term Safety and Efficacy of Mexiletine for Patients With Skeletal Muscle Channelopathies

Clinical and electrocardiogram data of 63 patients with non-dystrophic myotonias or hyperkalemic periodic paralysis due to CLCN1 or SCN4A mutations treated with mexiletine were analyzed retrospectively. Mexiletine doses ranged between 50 to 600 mg per day. Heart rate, PR interval, QRS duration, and corrected QT interval were calculated for each patient.

Patients with CLCN1 mutations tended to require higher doses of mexiletine as compared to those with SCN4A mutations. No serious adverse were identified with a mean follow up of 4.8 years per patient. Mexiletine did not change any of the cardiac parameters from their baseline measurements. Dyspepsia was the main side effect identified, occurring in 35% of patients.

Comment: Neuromuscular physicians often approach mexiletine initiation with trepidation, because the medication may lead to cardiac arrhythmias. No arrhythmias or alterations in EKG parameters were identified in this study, but it should be noted that it was small and retrospective, and vigilance concerning potential arrhythmia should not be relaxed.

Gender as a Modifying Factor Influencing Myotonic Dystrophy Type 1 Phenotype Severity and Mortality: A Nationwide Multiple Databases Cross-Sectional Observational Study
Felix Rougier et al. PLOS ONE DOI:10.1371/journal.pone.0148264

This is a cross sectional study of the French DM-Scope nationwide registry of adult DM1 patients (1409 patients of which 660 were men and 749 were women). Two other databases of patients with type 1 myotonic dystrophy were used to confirm the observations. These were the French DM1 patient survey (FDM-S) and the French National Health Service Database (PMSI). The objective of this study was to determine if gender is an influencing factor of phenotype severity, morbidity, and mortality. Several parameters including strength (using a converted 11 point MRC scale), severity of myotonia (time to open hand after contraction of or greater than 3 seconds), respiratory failure, cardiac conduction block, abnormal ECG, dysphagia, body mass index, among others were evaluated. The authors found that men were more likely to have developmental/educational abnormalities, severe myotonia, cardiac and respiratory involvement, and muscle weakness compared to women. Women had a higher risk of cataracts, dysphagia, digestive tract dysfunction, incontinence, thyroid disorder, and obesity. The analysis of the two additional databases (which had 970 and 3301 patients respectively) confirmed these findings (p<0.0001 to <0.01). Of interest in the FDM-S, 45% of men and 37% of women with DM1 had conduction abnormalities. This complemented the finding of 44.4% of men and 37.7% of women who had ECG abnormalities seen in the DM-Scope nationwide registry.

Comment: This study showed that there are gender differences in the phenotype of myotonic dystrophy type 1 that can be taken into consideration in sex-oriented care, risk stratification and for the future development of clinical trials.
Neurofilaments in the Diagnosis of Motoneuron Diseases: a Prospective Study on 455 Patients

In this prospective study, cerebrospinal fluid (CSF) and serum was collected from 455 patients: 253 patients with clinically definite or probable ALS or PLS, 85 with motor neuron disease mimics, and 117 with other neurodegenerative diseases. Elevated CSF but not serum neurofilament light chain (NfL) and phosphorylated heavy chain (pNfH) levels were found much more frequently in patients with motor neuron disease than in the comparison groups. A NfL cutoff level of 2200 pg/ml yielded a 77% sensitivity, 85% specificity, and 87% positive predictive value while a pNfH cutoff level of 560 pg/ml yielded an 83% sensitivity, 77% specificity, and 82% positive predictive value. Neurofilament levels were found to be elevated at earlier stages of the disease and to show a correlation with disease progression and duration.

Neurofilament Levels as Biomarkers in Asymptomatic and Symptomatic Familial Amyotrophic Lateral Sclerosis

Serum and cerebrospinal (CSF) fluid neurofilament levels were investigated as potential ALS biomarkers in three subject groups: patients with familial ALS (patients, N = 64), asymptomatic familial ALS gene mutation carriers (carriers, N = 12), and first-degree relatives of mutation carriers without mutations themselves (controls, N = 19). Serum and CSF NfL and pNFH were increased tenfold in patients compared to both carriers and controls, but no differences were identified between carriers and controls. Consistent differences in NF levels were not identified between patients with C9orf72 and SOD1 mutations. Clear correlations between disease duration and severity and neurofilament levels were not identified in this study.

Comment: ALS biomarkers are desperately sought to help with definitive disease diagnosis, to offer insights into disease pathophysiology, and to serve as outcome measures in clinical trials. Neurofilaments are critical structural proteins in the central nervous system, and abnormalities are hypothesized to play a role in the pathogenesis of a variety of neurodegenerative diseases. They are potentially relevant to ALS because they are found within the ubiquitinated cytoplasmic inclusions of TDP43. The two studies summarized above investigate the use of neurofilament levels as biomarkers for motor neuron disease. The sensitivity, specificity, and positive predictive value were good in the first study; prospective data collection in patients referred specifically for an ALS diagnosis would be a logical next step. While neurofilament levels were not useful as markers of disease progression in the second study, analysis of longitudinal data points in the same subject may disclose a more obvious relationship.
The NorthStar Ambulatory Assessment in Duchenne Muscular Dystrophy: Considerations for the Design of Clinical Trials

This retrospective study looks into the natural history of motor function in ambulatory boys with Duchenne Muscular Dystrophy (DMD) using the North Star Ambulatory Assessment (NSAA), a 17-item tool that assesses motor function in ambulant boys with DMD. The NSAA has a possible raw score of 0-34 and a linearized version of 0-100 (higher meaning greater function). Using the United Kingdom’s North Star Network data repository, a retrospective analysis of 513 ambulatory UK boys aged 3-16 years old from 2004-2012 was performed. To better understand the natural history using the current standard of care, differences between those boys who had initiated corticosteroids early (before age 5) and later (5-6.5 years old) and by genotype were evaluated. It was found that overall, until the age 7 the boys who were started on steroids typically gained 4 linearized units on the NSAA per year. However, the early starters of corticosteroids experienced greater gains, increasing by 7 linearized units per year, ultimately peaking at 73.8 for the early glucocorticoid users and 68.7 in the late starter group. On average, the boys then experienced an overall rate of decline of 8 linearized units per year thereafter (a change of 10 units being clinically significant), with the median age for loss of ambulation occurring at 13 years old. In a substudy using both Italian and UK data sets, exon 53 and 51 skippable deletions progressed more rapidly, losing 22 and 13 linearized units per year respectively while deletions skippable by exon 44 and 46 followed a more mild course than the average, declining only 9 linearized units over 2 years.

Comment: This study helps quantify the motor gains expected of boys with DMD undergoing both early and late glucocorticoid therapy and can serve as a gauge the standard of care and declines experienced by ambulatory boys with DMD using the NSAA tool; future studies may use this information to gauge the response to therapeutic trials compared to the natural history using the current standard of care. Additionally, the quantification of declines based on genotype will provide further aids in knowing the disease course in patients.

Recognition and Management of Acute Flaccid Myelitis in Children

This is a retrospective study of 11 children from the US Intermountain West Region between the ages of 13 months and 14 years of age who presented with acute flaccid myelitis between the time period of February 2014 and January of 2015. 10/11 patients had involvement of at least one limb. The 11th patient had only cranial nerve involvement. A core feature of this disorder were T2 hyperintensities involving the anterior horn cells. one-third of the patients also had involvement of brainstem and cerebellar nuclei. All patients had an abrupt onset followed by deterioration. Although most had CSF pleocytosis, it was not a feature in all patients. All received at least one modality of immunosuppressive therapy with approximately half receiving more than one immunosuppressive therapies (IVIG, PLEX, high dose pulse methylprednisolone). Unfortunately, also a core feature of this disorder is the chronic loss of function in at least one limb (only the patient who presented with solely cranial nerve involvement recovered completely). Although occurring at the time there was a spike in the incidence of enterovirus D68 infections, none of the patients were positive for this agent.

Comment: One point to be taken from this study is the importance of early imaging in pediatric patients who present with acute flaccid myelitis. The finding of T2 hyperintensities in the anterior horn cell region is a characteristic finding and can be distinguished from other disorders that can present similarly such as transverse myelitis and AIDP. Communication with the primary author of the study clarified that this is a separate population (from a different state) than results also of 11 children published in a different journal from the same period of time. This study confirms the poor prognosis of return to complete function of an affected limb with acute flaccid myelitis.
Positive Effects of Bisphosphonates on Bone and Muscle in a Mouse Model of Duchenne Muscular Dystrophy

Patients with Duchenne muscular dystrophy (DMD) are at risk for reduced bone mineral density and fracture secondary to inactivity. To determine if antiresorptive bisphosphonates could improve bone quality and muscle health, the authors studied Mdx mice treated with pamidronate during peak bone growth. Twenty mice were randomly assigned into bisphosphonate (BP) and untreated control groups. At 5 and 6 weeks of age, BP mice received pamidronate 2 mg/kg twice per week. At 13 weeks, the BP mice showed increased cortical bone density, femur strength, and fracture resistance in long bones but not in vertebral bodies. Pamidronate treatment also had positive effects on muscle: serum creatine kinase was reduced, muscle histology was improved, and grip strength was increased. Diaphragm function, however, did not improve.

Comment: This study supports a possible beneficial effect of pamidronate on bone and muscle health in the Mdx mouse. The improvement in bone density is consistent with previous retrospective work in human subjects. The identification of improved muscle structure and function with pamidronate is a novel finding that will require reproduction and further exploration.
Seropositivity for NT5c1A Antibody in Sporadic Inclusion Body Myositis Predicts More Severe Motor, Bulbar and Respiratory Involvement


Beyond muscle biopsy, clinically useful biomarkers for sporadic inclusion body myositis (sIBM) have been lacking. NT5c1A is a 43 kD protein that is abundant in skeletal muscle, and antibodies to this protein are frequently elevated in individuals with sIBM, with a sensitivity of 70% and specificity of 90%. This study investigates the relationship of NT5c1A antibodies to disease phenotype in individuals with sIBM. In this cross sectional study, 25 consecutive patients, 19 with definite and 6 with probable sIBM, underwent serological testing for the NT5c1A antibody through Western blot and confirmatory ELISA assays. The seropositive patients were more severely affected, requiring more time to arise from a chair (15.2 versus 2.3 seconds in the seronegative group), reduced MRC sum scores, increased odds of requiring a walker or wheelchair (61% vs 0%), dysphagia (89% vs 43%), and reduced FVC (82% vs 92% of predicted).

Comment: Greater levels of disability, dysphagia, and respiratory involvement are found in NT5c1A seropositive sIBM patients. These results suggest that closer monitoring of these patients for respiratory dysfunction may prove important. Antibody status may also prove important in clinical trial design and interpretation.

Guillain-Barré Syndrome Outbreak Associated With Zika Virus Infection in French Polynesia: a Case-control Study


In this case-control study, 42 patients who presented with Guillain-Barré syndrome (GBS) to a single referral center in French Polynesia were compared to a cohort of patients presenting to the same center without a recent febrile illness. Among the GBS patients, 98% had positive Zika virus antibodies, compared to only 56% of patients in the control group. 88% of the GBS patients reported a viral illness a median of 6 days prior to their presentation. The GBS patients typically reached a nadir quickly (in 6 days) and 38% had disease severe enough to require ICU admission. Electrophysiologic data showed predominantly axon loss suggestive of acute motor axonal neuropathy (AMAN). Glycolipid antibodies were present in 31% of GBS patients at admission, most commonly to GA1. Zika virus proteins and GA1 did not demonstrate cross reactivity. Three months after discharge 57% of GBS patients were ambulatory without assistance.

Comment: Zika antibodies were more likely to be present in patients with GBS than in control subjects, suggesting an etiologic role for Zika virus. This study provides important information about electrophysiology and clinical course in GBS patients. Whether similar findings will be reproduced in patients in the recent South American Zika outbreak is unclear.
Safety and Clinical Effects of Mesenchymal Stem Cells Secreting Neurotrophic Factor Transplantation in Patients With Amyotrophic Lateral Sclerosis Results of Phase 1/2 and 2a Clinical Trials

This article presents the results of a single-arm, open-label, proof-of-concept trial of the administration of mesenchymal stem cells (MSC) induced to become MSC-NFT with enhanced secretion of neurotropic factors (NFT) in patients with ALS. The initial phase of the trial involved a single intramuscular or intrathecal administration of autologous MSC-NFT. After an interim safety analysis of 12 patients, the trial was transformed into a dose escalating study in which an additional 14 patients were included. The rate of progression of the forced vital capacity and of the ALS Functional Rating Scale-Revised score in the IT (or IT+IM)-treated patients were slowed during the 6 months following MSC-NTF cell transplantation vs the pretreatment period. The most common side effects were headache, fever, vomiting, and leg and neck pain. There were two deaths not related to the treatment (suicide and hyponatremia).

Comment: This study supports safety and short-term efficacy of IT and IM administration of autologous MSC-NTF. The suggestion of improvement of FCV and ALSFRS needs to be confirmed with larger and longer-duration clinical trials.

A Randomized Trial of Mexiletine in ALS. Safety and Effects on Muscle Cramps and Progression

Weiss and colleagues report a randomized double-blind placebo-controlled trial of mexiletine for the treatment of muscle cramps and disease progression in ALS. The primary outcome of this trial was to determine both the safety and tolerability of mexiletine. The secondary outcome was to evaluate the pharmacokinetics of mexiletine, disease progression, and muscle cramp frequency and severity. Sixty patients were included in the study and randomized to receive either placebo, 300 mg of mexiletine, or 900 mg of mexiletine divided in two doses daily for 12 weeks. Compared to controls, the 300 mg mexiletine group experienced a 30% reduction in cramp frequency, and the 900 mg group a 16% reduction. Cramp intensity was also reduced by 45% in the 300 mg group and by 25% in the 900 mg group. Six (32%) of patients in the 900 mg group discontinued the drug due to side effects, versus 1 patient in the 300 mg group. There was no difference in the ALFSRS or vital capacity in the mexiletine-treated patients compared to control subjects.

Comment: This study shows evidence that mexiletine is potentially effective for the treatment of muscle cramps in patients with ALS. Tolerability was better with the 300 mg daily dose. Mexiletine may prove a useful option for management of a symptom which is often difficult to control in ALS. Unfortunately, it did not seem to be effective in slowing disease progression.
Modulating Myosin Restores Muscle Function in a Mouse Model of Nemaline Myopathy

Nemaline myopathy is among the most common of the congenital myopathies. Approximately 20% of cases are caused by mutations in the ACTA1 gene which disrupts actin-myosin interactions and prevents effective cross-bridging. In this study, Lindqvist and colleagues generated a knock-in mouse model expressing the ACTA1 mutation, and identified muscle atrophy in these mice at 8 weeks. In the second part of the experiment, they injected intramuscularly an adeno-associated viral vector (AAV) with a myosin light chain 4 (MYL4) transgene into both transgenic and wild type mice. The transgene encodes MyLC1a/emb, a myosin isoform present only in embryo heart and skeletal muscles, and is capable of generating greater force than normal adult myosin. Injections were performed when the mice reached 4 weeks of age. When the transgene was injected into ACTA1 transgenic mice, there was an increase in both myofiber size and in isometric maximal force-producing capacity when compared with those mice injected with a control vector. Furthermore, wild type mice showed an increase in contractility when injected with the MYL4 transgene.

Comment: The authors demonstrated increased myofiber size and force generation in myocytes of ACTA1 transgenic mice injected with the gene encoding the MyLC1a/emb isoform. The injections were performed 4 weeks prior to the anticipated myocyte atrophy. A next logical next step, therefore, would be to perform the injections after myocyte atrophy has already been identified, a strategy that would more closely parallel potential human applications. The authors hypothesize that the MYL4 transgene might also be applied to nemaline myopathy caused by gene defects in other contractile proteins. Because wild type mice also demonstrated an increase in contractility, gene therapy with this MYL4 transgene could be effective for muscle disorders other than the nemaline myopathies.

Identifying Who Will Benefit From Non-invasive Ventilation in Amyotrophic Lateral Sclerosis/Motor Neurone Disease in a Clinical Cohort

Over the last 15 years, non-invasive ventilation (NIV) has seen increasing use for patients with amyotrophic lateral sclerosis (ALS) with the goal of prolonging survival and slowing respiratory decline. In this retrospective analysis from a subspecialty center in Australia, investigators sought to quantify the effect of NIV on survival and respiratory function decline across different ALS. Data collection occurred from 1991 through 2011; the providers began routinely prescribing NIV in 2002. 929 patients with ALS-bulbar onset, ALS-cervical onset, ALS-lumbar onset or flail limb were included in the study; 219 received NIV and 711 did not. Using both univariate and multivariate Cox-regression analysis (to account for percutaneous endoscopic gastrostomy placement, riluzole use, age of onset and gender), median tracheostomy-free survival increased from 15 months to 28.63 months across all phenotypes, an increase of 90%. The survival for ALS-bulbar onset patients increased from 13.57 to 32.61 months, an increase of 140%. NIV also reduced rates of decline of forced vital capacity (FVC), forced expiratory volume in one second (FEV1), maximal inspiratory and expiratory pressures (MEP and MIP, respectively).

Comment: This retrospective study involving a large cohort of patients with ALS spans the period where NIV became commonly prescribed for patients with ALS. It bolsters the evidence to support NIV prescription in patients with ALS, prolonging survival by 90% across all phenotypes and 140% for bulbar-onset patients and slowing the rate of respiratory decline.
Idebenone is a short chain benzoquinone with well-known antioxidant properties. This article reports the data from a multi-center Phase III randomized controlled trial to study the effects of Idebenone in patients with Duchenne Muscular Dystrophy (DMD Long-term Idebenone Study, DELOS). Patients enrolled had to be either steroid naïve or off-steroid for at least 12 months. The DELOS trial mainly measured the incidence of bronchopulmonary adverse events (BAEs) and the need for systemic antibiotics in the duration of the study (52 weeks). BAEs consisted of upper respiratory tract infections, bronchitis, pneumonia, cough, Influenza with respiratory symptoms, viral infection with respiratory symptoms, acute respiratory failure, dyspnea, laryngitis, and respiratory failure. 64 boys with DMD between the ages of 10 and 18 years old who were largely in the non-ambulatory phase of their disease were randomized into a placebo group (33 boys) and a 900mg/day Idebenone group (31 boys) with the placebo group being slightly older (15 years vs 13.5 years). 6 patients had 7 BAEs in the Idebenone group as compared with 17 patients with 28 BAEs in the placebo group. 7/31 boys had 8 events requiring the need for systemic antibiotics in the Idebenone group in comparison to 13/33 boys with 17 events in the placebo group. Furthermore, patients in the placebo group used systemic antibiotics for longer (105 days) compared to patients in the idebenone group (65 days). Therefore, it was concluded that the use of Idebenone appears to decrease the incidence of both BAEs and need for systemic antibiotics in patients not treated with steroids between the ages of 10-18 years.

Comment: Progressive loss of respiratory function leading to restricted pulmonary disease is a significant cause of morbidity and mortality in DMD patients. This DELOS trial showed that Idebenone at 900 mg/day oral dosing provides statistically significant benefits to protect the respiratory function and slow the progression of pulmonary disease compared with placebo in steroid naïve or steroid-off DMD patients over a 1-year study period. It broadens our therapeutic approaches to this devastating disease. Data from studies in patients who are taking Idebenone and steroids concomitantly would be very helpful.

Gain of Toxicity from ALS/FTD-Linked Repeat Expansions in C9ORF72 Is Alleviated by Antisense Oligonucleotides Targeting GGGGCC-Containing RNAs


Hexanucleotide (GGGGCC) expansions in C9ORF72 (abbreviated to c9 often) are the most frequent genetic cause of ALS/FTD. Jiang et al focused on the disease mechanisms of this mutation. They evaluated mice expressing C9ORF72 RNAs with up to 450 GGGGCC repeats or with one or both C9orf72 alleles inactivated. Their data showed that chronic 50% reduction of C9ORF72, as reported in c9ALS/FTD patients was well tolerated without signs of disease, while its absence produced splenomegaly, enlarged lymph nodes, and mild social interaction deficits, but not motor dysfunction.

Then they studied transgenic mice that express a bacterial artificial chromosome (BAC) carrying the human expanded c9ORF72 gene from a c9ALS patient. These hexanucleotide expansions caused in these mice accumulation of RNA foci and dipeptide-repeat proteins that is age-, repeat-, length-, and expression-level-dependent, resulting in increased anxiety and impaired cognitive function.
Single-dose intrathecal injection of antisense oligonucleotides (ASOs) that target these mutated RNAs but preserve levels of mRNAs encoding C9ORF72 produced sustained reductions in RNA foci and dipeptide-repeat proteins, and ameliorated the behavioral deficits.

**Comment:** Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are two devastating neurodegenerative diseases with distinct clinical symptoms but common pathological features and genetic causes. Several mechanisms have been proposed including loss of c9ORF72 protein function and gain of toxicity. Jiang et al elegantly identified gain of toxicity as a main pathogenesis of GGGGCC-expanded C9ORF72 for ALS/FTD. They also proved the feasibility and effectiveness of antisense oligonucleotides-mediated therapy.

Mouse models for ALS have been desirable for decades. In the same issue of *Neuron*, Liu et al also reported development of a c9orf72 BAC mouse model that can be used for future research to develop targeted therapies for ALS/FTD. [Neuron. 2016 May 4;90(3):521-34. doi: 10.1016/j.neuron.2016.04.005. Epub 2016 Apr 21. C9orf72 BAC Mouse Model with Motor Deficits and Neurodegenerative Features of ALS/FTD. Liu Y, Pattamatta A, Zu T, Reid T, Bardhi O, Borchelt DR, Yachnis AT, Ranum LP.]
Association of a Locus in the CAMTA1 Gene With Survival in Patients With Sporadic Amyotrophic Lateral Sclerosis

The objective of this study was to identify genes which might influence ALS survival using genome-wide association studies (GWAS). A total of 4256 patients were included, 29.8% had bulbar onset with a mean survival of 27.5 months and 70.2% had spinal onset with a mean survival of 35.9 months. Two loci were associated with decreased survival. At locus 10q23 the presence of the SNP rs139550538 AA or AT genotype was associated with an 8-month reduction in survival. At locus 1p34 the presence of SNP rs2412208 GG or GT, which fell within the CAMTA1 (calmodulin binding transcription activator 1) gene, was associated with a 4-month reduction in survival.

Comment: This study identified two gene variants associated with decreased survival in ALS. Identifying genes that affect survival in ALS could aid us in better understanding the biology of the disease and, possibly in identifying possible gene targets for intervention. As with all GWAS studies, caution must be applied when interpreting the results, as the pathogenic roles of genes encoded at these loci in ALS are not known.

Randomized Trial of Thymectomy in Myasthenia Gravis

A single-blind randomized trial (rather-blinded) of thymectomy was performed in 126 non-thymomatous adults with myasthenia gravis of less than 5 years duration and Myasthenia Gravis Foundation of America clinical classifications of II to IV. Thymectomy was performed within 1 month of randomization by median sternotomy. Both groups were placed on increasing prednisone immediately after randomization until there was minimal disease activity present. Once minimal manifestation of disease was achieved, prednisone was tapered. Intravenous immunoglobulin and plasma were allowed for exacerbations. Azathioprine or cyclosporine were allowed for refractory cases. Patients who underwent thymectomy demonstrated significantly lower (improved) Quantitative Myasthenia Gravis at 3 years. The time-weighted average prednisone dose was also significantly lower in the thymectomy group (alternate day dose of 44 mg vs 60 mg). There was no difference in treatment association complications (including death) between the groups. Fewer patients in the thymectomy group were hospitalized due to exacerbation than the prednisone alone group (9% vs 37%).

Comment: Although thymectomy has been performed for many years in patient with myasthenia gravis and assumed to be beneficial, it has been challenging to prove its efficacy. This study demonstrates a clear clinical benefit of thymectomy in patients with non-thymomatous myasthenia gravis. The relatively high prednisone doses at the conclusion of the study are due partially to restriction of steroid-sparing agents by the study protocol. An interesting modification of this study, therefore, might be a study of thymectomy compared to “maximum medical therapy” with the addition of an agent such as azathioprine, cyclosporine, or mycophenolate mofetil.
Rate of Disease Progression: A Prognostic Biomarker in ALS

The ALSFRS-R is a commonly used clinical biomarker to monitor function in patients with ALS but does not account for the rate of disease progression, which is an independent predictor of survival. A previous study of 82 patients with ALS in Japan investigated the rate of disease progression (ΔFS) at the initial visit as a biomarker using the following formula:

\[
\Delta FS = 48 - \frac{\text{Total ALSFRS-R at initial visit}}{\text{Symptom duration (months)}}
\]

Higher numbers, therefore, indicate faster progression. Building upon this initial work, clinicians in this Australian study recruited a cohort of 203 patients with possible, probable, or definite ALS between 2004 and 2014, of whom 164 met inclusion criteria. Using history obtained from the patient and family members, rate of disease progression was calculated. The primary end point was survival. Statistical analysis were used to define rate of progression cutoff values of <0.47 (slower progression), 0.47-1.11 (intermediate progression), and >1.11 (faster progression). Median survival time from the initial visit was 2.4 years for the slow progressing group, 1.6 years for the intermediate group, and 0.7 years for the fast progressing group. Age 70 years or greater, shorter duration of symptoms, lower total ALSFRS-R score, ALSFRS-R respiratory subscore <10, and bulbar onset disease at initial visit were associated with worse prognosis.

Comment: While the conclusion that a faster rate of progression at initial assessment of a patient with ALS portends a poorer prognosis is intuitive, this study provides more precise quantification of this phenomenon. Discriminant points were defined, and these could be employed in the clinic, and possibly to define groups of slow, intermediate, and fast progressing patients for clinical trial purposes. Caution must be used in applying these results, as substantial errors might be made in computing the denominator of ΔFS.

Clinical Characteristics of Patients With Double-Seronegative Myasthenia Gravis and Antibodies to Cortactin

The objective of this retrospective cohort study of patients with myasthenia gravis was to determine the characteristics of patients negative for both acetylcholine receptor antibodies (AchR Ab) and MuSK antibodies and positive for cortactin antibodies and compare them with seropositive patients. A total of 250 patients were included; 80% (201) were AchR-Ab positive, 4.4% (11) were MUSK-Ab positive and 15.2% (38) were double seronegative. Nine out of the 38 double seronegative patients were positive for cortactin antibodies. These patients tended to be younger than those with AchR Ab myasthenia gravis and had milder disease: none of the cortactin positive patients had bulbar symptoms, six had pure ocular symptoms, and three had mildly generalized myasthenia gravis.

Comment: Cortactin is a post synaptic neuromuscular junction protein involved in acetylcholine receptor clustering. Though not yet proven to be pathogenic, antibodies to cortactin can be added to the list of antibodies described in patients with double seronegative myasthenia gravis LRP4, agrin, and Dok-7 subgroup. The milder disease phenotype in patients with cortactin antibodies needs to be confirmed in larger samples.
Myasthenia Gravis Treated With Autologous Hematopoietic Stem Cell Transplantation

The authors report a series of seven patients (two of whom were seronegative) with severe myasthenia gravis treated with autologous hematopoietic stem cell transplantation. Patients were refractory to treatment with multiple treatment modalities including pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, intravenous immunoglobulin, plasma exchange, and thymectomy. The protocol included graft mobilization and purification, treatment with intensive conditioning chemotherapy, and graft reinfusion. All patients achieved complete stable remission with no residual myasthenia gravis symptoms or requirement for disease-modifying therapy.

Comment: Refractory myasthenia gravis accounts for 10% of disease. Hematopoietic stem cell transplantation offers a potential treatment option for patients in this group. It should be emphasized that this study is a retrospective case series, and that stem cell transplantation has not been studied in a prospective fashion in patients with myasthenia gravis.

High Risk of Cancer in Autoimmune Necrotizing Myopathies: Usefulness of Myositis Specific Antibody

Allenbach and colleagues investigated the incidence of cancer in patients with necrotizing autoimmune myopathies. A cohort of 115 patients was divided into those with anti-signal recognition particle (SRP) antibodies (49 patients), anti-HMGCoA reductase (HMGCR) antibodies (52 patients), and seronegative (SN) necrotizing autoimmune myopathies (14 patients). These patients were considered to have a synchronous cancer if the cancer was diagnosed up to 3 years before or the after the diagnosis of myopathy. Malignancies were identified in 28.6% of SN patients, 17.3% of HMGCR patients, and 8.1% of SRP patients. The cancer risk compared to an age- and sex-matched population was 8.35 for the SN patients, 2.79 for the HMGCR patients, and 1.65 for the SRP patients. No specific cancer was identified as being particularly common in any of the groups or in the population with necrotizing autoimmune myopathy as a whole.

Comment: The association of cancer with inflammatory myopathies, particularly dermatomyositis, is well known. It is hypothesized that an anti-tumor immune response is etiologically related to the myositis. This study sheds light on the relationship between necrotizing autoimmune myopathy antibody status and malignancy. Clear increases in cancer risk with HMGCR antibodies and seronegative patients were identified. Although the authors found that the rate of cancer in SRP antibody patients was not statistically greater than a matched population, some caution needs to be exercised before abandoning cancer screening in this group. Unfortunately, the study did not identify any specific cancer as being frequently associated with necrotizing autoimmune myopathies, a finding that precludes a targeted screening strategy.
A Comparison Between IVIg and Plasma Exchange as Preparations Before Thymectomy in Myasthenia Gravis Patients

A small randomized study was conducted in patients with myasthenia gravis who were scheduled to undergo thymectomy. Twenty-four patients were randomized to receive either IVIg 1 g/kg/day x 2 consecutive days or plasma exchange 5 times every other day. Treatments were administered between 10-30 days before the procedure. Post-operative intubation was more common and duration of treatment was longer in patients treated with plasma exchange. There were no differences in duration of hospitalization, length of ICU stay, or post-operative corticosteroid dose between the two groups.

Comment: Although a small study, this report suggests that IVIg and plasma exchange may be comparable preparatory treatments for patients undergoing thymectomy. Traditionally, plasma exchange has been employed as the pre-thymectomy treatment of choice, but the greater convenience of administering IVIg may make it the preferred treatment in anticipation of thymectomy.