News Science Anthology
February 2018 - December 2018

Articles on NM and EDX medicine selected by the AANEM News Science Editorial Board
Anthology of NSEB Journal Article Summaries and Comments
February 2018 - December 2018

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February 8, 2018

Draak THP, Faber CG, Merkies ISJ. Quality of life in inflammatory neuropathies: the IN-QoL. J Neurol Neurosurg Psychiatry. Published Online First: 06 October 2017. doi: 10.1136/jnnp-2017-316634

Submitted by Francisco E. Gomez, MD
Edited by Lisa M. Williams, MD

While there is a multitude of quality of life (QoL) questionnaires developed for chronic diseases, to date, there is no consensus on which questionnaire is best suited to assess QoL in inflammatory neuropathies. This study used an international cohort involving 264 patients diagnosed with GBS, CIDP, IgM monoclonal gammopathy related polyneuropathy (MGUSP) and Multifocal Motor Neuropathy (MMN) to establish a new disease-specific questionnaire in inflammatory neuropathies (IN-QoL). The cohort completed six commonly used questionnaires including the WHO quality of life scale (WHOQoL BREF), Sickness Impact Profile, EuroQoL scale, Nottingham Health Profile, short form 36-item health survey (SF-36) and Vickrey Peripheral Neuropathy Quality-of-Life Instrument-97. Investigators then applied statistical methods including Rasch analysis to the pooled 324 questions, determining a final questionnaire which was slightly reliable, valid and responsive. The IN-QoL proved to be multidimensional requiring two subsets termed the In-QoL-mental and IN-QoL functional. However, when correlated with the patient’s visual analogue scale using the Euro-QoL-health quality visual analogue scale (EQ-VAS) the mental subset had a higher correlation. A higher responsiveness rate was associated with patients with acute disease such as GBS as opposed to more indolent diseases such as MGUSP or MMN.

Comment: The IN-QoL is a novel questionnaire evaluating reported QoL in inflammatory neuropathies and, in combination with the EQ-VAS, may be a useful assessment of QoL.
This study compared the performance of neuroimaging techniques (e.g. high-resolution ultrasound (HRUS)) and magnetic resonance imaging (MRI), when applied to the brachial plexus, as part of the diagnostic work-up of chronic inflammatory demyelinating neuropathy (CIDP) and multifocal motor neuropathy (MMN). MRI is an established adjunctive diagnostic tool while HRUS is a widely available quantitative bedside tool.

They enrolled 51 consecutive patients with CIDP (n = 24) or MMN (n = 27). The inclusion criterion was a diagnosis of CIDP and MMN (definite, probable and possible. They enrolled treatment naïve patients. Sonographic and MRI studies were performed prior to treatment. The treating physicians were blinded to the neuroimaging results. MRIs were rated by experienced neuroradiologists (blinded to results from HRUS and NCS studies). One author performed all sonographic examinations and was blinded to results from NCS and MRI studies.

Magnetic resonance imaging showed enlargement and/or a pathological T2-hyperintense signal of the brachial plexus in 17/23 (74%) patients with CIDP and 14/28 (50%) patients with MMN. MRI of the brachial plexus was normal in 20/51 (39%) enrolled patients.

HRUS found sonographic enlargement of a brachial trunk (superior, median or inferior) in 18/23 (78%) patients with CIDP and 19/28 (68%) patients with MMN. MRI was normal in 4/23 (17%) patients with CIDP and 8/28 (29%) patients with MMN with an abnormal HRUS. Applying both MRI and HRUS identified 20/23 (87%) patients with CIDP and 22/28 (79%) patients with MMN, further enhancing the diagnostic performance of neuroimaging (from 61–73% to 83%).

Comment: The high level of concordance seen in this study suggests that both MRI and sonography of the brachial plexus can be used to support the clinical suspicion of an inflammatory neuropathy.

The study indicates that brachial plexus sonography complements MRI in the diagnostic work-up of patients with suspected CIDP and MMN. Therefore, combined imaging studies could, in the future, be included in the revised diagnostic consensus criteria for chronic inflammatory neuropathies to enhance diagnostic performance. The brachial plexus abnormalities seen on imaging did not aid in further differentiating between CIDP and MMN. The exact pathological or electrophysiological correlates of imaging abnormalities are largely unknown and require further study.
Control of the human arm and hand are eloquently orchestrated by sensory and motor nerves arising from the cervical spinal cord. To date, the exact quantity of sensory and motor axons responsible for upper limb control are not known. The researchers of this study used 9 human heart-beating organ donors to perform a quantitative analysis of the nerve segments from the trunks and cords of the brachial plexus and segments of the major nerves arising from the cervical spinal cord. Motor and sensory axons were identified by the presence in histologic specimens of choline acetyltransferase (ChAT) and neurofilament. Using double immunofluorescence staining, the researchers were able to distinguish large diameter axons, arising from alpha motor neurons, and small diameter axons, arising from gamma motor neurons and preganglionic sympathetic neurons. The results of this study determined that only 10% of the 350,000 axons emerging from the spinal cord to innervate the upper limb were large diameter. Sensory axons outnumbered motor axons by a ratio of 9:1. Additionally, sensory axons were found to increase as in proportion distally towards the hand.

Comment: This study is the first to quantify the motor and sensory axonal components of the upper limb elucidating predominant afferent sensory control needed for fine activities such as finger motions of the upper limb, rather than abundance of motor axons.
This study evaluated a group of 200 pediatric patients (ages 3-20 years) with genetically classified types of Charcot-Marie-Tooth (CMT) disease assessed serially over a 2-year period using the CMT Pediatric Scale (CMT PedS). This is a validated Rasch-built disability scale which evaluates gross and fine motor function, strength, sensation, and balance. The 4 most common genetic types were 58% CMT1A, 5% CMT1B, 4% CMT2A, and 4% CMT4C. The study provides information about the rate of natural progression of deficits in the CMT subtypes.

**Comment:** The following conclusions were reached in this study:

1. CMT PedS is sensitive to progress of CMT.
2. The rate of progress differed between most common subtypes of CMT.
3. Children with CMT deteriorate significantly over a 2-year period.
March 26, 2018


Submitted by David R. Mayans, MD

Edited by Lisa M. Williams, MD

This study was a double-blind, sham controlled phase 3 trial of Nusinersen with primary endpoints of motor milestone response and event free survival. Nusinersen is an antisense oligonucleotide drug that modifies pre-mRNA splicing of SMN2 to promote increased production of SMN protein. This medication is given in a series of intrathecal injections. Initially, 80 patients were randomized to the Nusinersen group and 41 controls with follow-up up to 394 days. The average age at first dose was 163 days (5 months). In an interim analysis, the motor milestone response was 41% to 0% in the control group so the trial was terminated early. The final analysis included all 121 infants. 51% of patients in the Nusinersen group had motor-milestone response, 22% had head control, 8% could sit, and 1% could stand. None in the control group reached any of these milestones. At the time of final analysis, 39% in the Nusinersen group had died or gone on permanent assisted ventilation compared to 68% of the control group. An increase in the CHOP INTEND scale was seen in 73% of patients on Nusinersen compared to 3% in control. 36% of patients in the Nusinersen group had an increase in peroneal and ulnar CMAP compared to 5% in the control group. In subgroup analysis, patients who received this at a younger age had better outcomes than those at a later age.

Comment: This is an important study that helps validate a previous phase 2 trial of Nusinersen for use in spinal muscular atrophy type 1. This medication not only prevents motor decline but also has improvements in motor milestones which has not been seen before in SMA. The treatment appears to be safe and is more effective if started early in the disease. It would be interesting to see a combination of therapy of Nusinersen and adeno-associated virus serotype 9 gene replacement therapy for the combined effect.
March 26, 2018


Submitted by David R. Mayans, MD
Edited by Nandita S. Keole, MD

Spinal muscular atrophy (SMA) type 1 is a devastating illness of the motor neurons presenting in early childhood. Symptoms are usually present at 1 month of age, and by 20 months of age, only 8% survived without ventilatory support. In this study, 15 children with genetically confirm SMA1 (homozygous SMN1 exon 7 deletions and two copies of SMN2) were selected for administration of an adeno-associated virus serotype 9 carrying SMN complementary DNA encoding the missing SMN protein. The Mean age was 6.3 yrs (5.9-7.2). Patients were enrolled in 2 cohorts: 3 at a low dose, and 12 at a high dose. The AAVS9 was delivered in a one-time dose intravenously. The primary outcome was safety of the infusion. The initial cohort of 3 was given the low dose which was tolerated well, so the dose was increased for the second cohort which was recruited at a later time. Secondary outcomes included time until death, need for permanent ventilatory support, and motor milestone achievements using the CHOP INTEND (Children’s Hospital of Philadelphia Infant test of NM disorders) scores. The mean age of treatment was 6.3 months in the first cohort and 3.4 months in the second cohort. The first patient had elevated ALT and AST, so the protocol was changed to allow for Prednisolone around the time of administration which attenuated elevations in other patients. 2 other patients required extra prednisolone due to elevations of liver enzymes. All patients had reached 20 months of age and none required permanent ventilatory support. Patients in both cohorts had significant increases in CHOP INTEND scores (7.7 in cohort 1 and 24.6 in cohort 2) with most being able to maintain a score more than 40. 9 of 12 patients in cohort 2 could sit unassisted for 30 seconds. 11 of 12 achieved head control. 2 were able to crawl, pull to stand, and walk independently. 11 of 12 had the ability to speak.

Comment: This is another groundbreaking study in the treatment of SMA with a targeted gene therapy used to replace the nonfunctional SMN gene. This treatment not only prevented the motor decline in the patients, but actually allowed them to have motor improvements and reach milestones not seen in this disease previously. It will be interesting in the future to see how this method may work in patients at an even younger age or if this could be used in combination with Nusinersen.

Submitted by Shan (Sarah) Chen, MD, PhD

Additional comments by David B. Rosenfield, MD

Contactin-associated protein-like 2 (CASPR2) is a neuronal adhesion molecule of the neurexin superfamily known to form a protein complex with shaker-type voltage-gated potassium channels such as Kv1.1 and Kv1.2. In fact, antibodies to VGKCC are not directed against Kv1 channels, but to the complex.

Human autoantibodies to CASPR2 have been associated with neuromyotonia and Morvan’s syndrome. A common feature in these patients is neuropathic pain. However, the mechanism by which CASPR2 modulates nociceptive function is unknown.

Dawes et al isolated CASPR2 autoantibodies from 2 patients with very high titers of CASPR2 IgG and injected them into healthy mice for 2 or 3 weeks. These mice had high CASPR2 titers at the end of the experiment and these antibodies were found mostly on the surface of sensory neurons, i.e., dorsal root ganglion (DRG), only some in the sciatic nerve, and none in spinal cord and they resulted in mechanical pain-related hypersensitivity in the absence of neural injury or overt inflammation.

Genetic knockout mice lacking CASPR2 (Cntnap2-/-) demonstrated enhanced pain-related hypersensitivity to noxious mechanical stimuli and heat. They showed that both primary afferent excitability and subsequent nociceptive transmission within the dorsal horn were increased in Cntnap2-/- mice.

They further demonstrated that CASPR2 regulates DRG excitability and membrane Kv1 channel expression at the soma membrane.

Dr. Chen’s Comments: Pain is one of the cardinal signs of inflammation. Increasing studies have been linking immune system to the pathogenesis of pain. Previously it was thought that autoantibodies cause tissue damage and inflammatory reactions.

This work showed that patient CASPR2-antibodies cause a loss of Kv1 channel membrane expression and hyperexcitability in DRG without nerve injuries or inflammatory responses. This is the first example of passive transfer of an autoimmune peripheral neuropathic pain disorder. This group further showed that either immune or genetic-mediated ablation of CASPR2 enhanced the excitability of DRG neurons in a cell-autonomous fashion through regulation of Kv1 channel expression at the soma membrane. Therefore, CASPR2 has a key role in regulating DRG excitability. Interestingly, CASPR2 mutations have been linked to autism spectrum disorders, in which sensory dysfunction is increasingly recognized. This work provides a rationale for testing CASPR2 antibodies in chronic pain patients and possible immunotherapy.

Also commented in “Autoantibodies Hurt: Transfer of Patient-Derived CASPR2 Antibodies Induces Neuropathic Pain in Mice” in the February 21, 2018 edition of *Neuron*.

Dr. Rosenfield’s Summary and Comments: All of us see patients with pain that is difficult to explain and treat. In this article in *Neuron*, the authors discuss that contactin-associated protein-like 2 (CASPR2) antibodies cause loss of Kv1 channel membrane expression and hyperexcitability in Dorsal Root Ganglion (DRG) without preexisting nerve injury or inflammation. These authors demonstrate in mice that one can passively transfer an autoimmune peripheral neuropathic disorder in which CASPR2 has an important role in regulating DRG excitability and posit that these antibodies might even have a role in autism spectrum disorders.
May 3, 2018


Submitted by Francisco E. Gomez, MD

Additional comments by David B. Rosenfield, MD

In this ambitious study, investigators sought to determine the role of sensory neuron – brain-derived neurotrophic factor (BDNF) – in the genesis of chronic pain. They included a group of mice in whom they ablated the expression of BDNF in dorsal root ganglia neurons, and a control. BDNF ablation had no effect on motor function, general pain perception or threshold and there were no significant differences in pain related behavior between the ablated and control groups. The BDNF ablated mice did show hyposensitivity to noxious heat.

Most notably, in chronic and neuropathic pain models, the BDNF ablated mice showed less nociceptive behavior and decreased mechanical hypersensitivity. Notably, upon injection of carrageenan (an inflammatory mediator), the experimental mice demonstrated much faster pain recovery in terms of mechanical hypersensitivity recovery.

Authors concluded that BDNF plays no part in acute pain perception, but does mediate chronic pain in some capacity. More importantly, they demonstrated that targeted gene ablation in specific cell population as a viable method of exploring therapeutic targets.

**Dr. Gomez’s Comments:** The importance of this study is twofold. First, it opens the door to a number of questions directly relevant to a number of patients who live with chronic pain. What is the role of BDNF in humans? Could it be a viable target for patients with neuropathy? What is the role of BDNF in the pathophysiology of Reflex Sympathetic Dystrophy? Is there hope for a new avenue of treatment for any of these patients? Additionally, the viability of selectively turning off single genes in specific cell populations is tantalizing, to say the least, in terms of the possibilities of new avenues for research.

**Dr. Rosenfield’s Summary and Comments:** This article in Brain demonstrates that brain-derived neurotrophic factor (BDNF) ablated mice had less nociceptive behavior and decreased mechanical hypersensitivity but that this substance may have a role in mediating chronic pain, possibly even in Complex Regional Pain Syndrome.
Small fiber neuropathy (SFN) is a common disorder leading to neuropathic pain and autonomic symptoms. The objective of this study was to investigate associated conditions in a large cohort of SFN patients and compare the prevalence to healthy individuals.

A total of 921 patients with pure SFN were screened according to a standardized comprehensive diagnostic algorithm and compared with literature findings. No associated condition could be found in 53% of the patients. Autoimmune diseases, sodium channel gene mutations, diabetes mellitus including glucose intolerance, and vitamin B12 deficiencies were more prevalent than reported literature findings, followed by alcohol abuse, chemotherapy, monoclonal gammopathy of undetermined significance, and haemochromatosis. In patients who were already known with a possible underlying condition at screening, additional underlying conditions were still found in another 26.7% of patients.

Based on these results, it is recommended that patients with pure SFN are screened at least for autoimmune diseases, sodium channel gene mutations, diabetes mellitus including glucose intolerance, and vitamin B12 deficiency, even when they already have a potential underlying condition at referral.

**Dr. Keole’s Comments:** This study was interesting because it highlights the causes of SFN.

**Dr. Rosenfield’s Summary and Comments:** The authors of this article remind us of the complex nosology of small fiber neuropathy (SFN). They reviewed a large cohort of SFN patients and note that 43% had at least 1 of the following: autoimmune diseases; sodium channel mutations, diabetes, B-12 deficiencies, alcohol abuse, chemotherapy, monoclonal gammopathy of undetermined significance and haemochromatosis, reminding us once again that the underlying nosology of SFN is extensive.
May 15, 2018


Submitted by David R. Mayans, MD

Additional comments by David B. Rosenfield, MD

Over the last year, we have highlighted a couple of articles involving Nusinersen as a novel treatment for spinal muscular atrophy (SMA). Another trial has been completed and the data was shared in this article. The initial trial data involved children with SMA type 1 diagnosed within the first 2-6 months. This trial involved patients diagnosed with SMA with symptom onset after 6 months of age and their age at the onset of the trial between 2 and 12. There were a few exclusion criteria including the need for invasive or non-invasive ventilation, contractures, severe scoliosis, or gastric tube.

Patients were divided into 2 treatment groups, less than 6 years of age and older than 6 years of age. They were randomly assigned in a 2:1 fashion to treatment with Nusinersen versus sham procedure. Nusinersen was administered on days 1, 29, 85, and 274. Eighty-four were assigned to the Nusinersen group and 42 were in the control group. The patients were followed for 15 months. The primary endpoint of the study was a change in the Hammersmith Functional Motor Scale-Expanded (HFMSE). An interim analysis showed a significant improvement in the treatment group compared to placebo so the trial was terminated early. More than half of the treatment group had a clinically significant improvement in the HFMSE score while only 26% of the placebo group had improvements.

**Dr. Mayans’ Comments:** This is another study adding to the growing body of evidence that Nusinersen is effective at not only slowing the progression of SMA, but leading to improvements in strength and gain of function in SMA patients. Previous studies looked at the SMA type 1 population showing effectiveness and safety of treatment starting under 6 months of age. This trial had older patients (average age of 3 years) and shows the effectiveness of this medication in an older SMA population. While this may seem like “old news” due to the studies on younger kids over the last year, this study and treatment are truly groundbreaking in the treatment of this disease.

**Dr. Rosenfield’s Summary and Comments:** In 2016, Nusinersen (marketed as Spinraza) became the first medication FDA approved for treating SMA. The medicine is intrathecally administered to treat SMA with a mutation in SMN1. SMA is caused by loss of function mutation in the SMN1 gene which codes for survival motor neuron (SMN) protein. Patients survive due to low amounts of the SMN protein produced from the SMN2 gene. Nusinersen modulates alternate splicing of the SMN2 gene, functionally converting it into an SMN1 gene, thus increasing the level of SMN protein in the CNS.
May 25, 2018


Submitted by Leigh Maria K. Ramos-Platt, MD

Additional comments by David B. Rosenfield, MD

In 2004, a committee of experts in the treatment of spinal muscular atrophy (SMA) (the majority associated with 5q11.2-q13.3) created a task force. The result of their collaboration was the 2007 published SMA Standards of Care (SOC) document. The SMA SOC likely resulted in improvement of natural history in all SMA types. With the current research climate and the approval of Nusinersen in December 2016, the SMA community recognized the need for the SMA SOC document to be updated. Nine areas of SMA care were addressed:

1. Diagnosis and genetics
2. Physical therapy and rehabilitation
3. Orthopedic care, growth, and bone health
4. Nutrition
5. Pulmonary care
6. Acute care in the hospital setting
7. Other organ involvement
8. Medication
9. Ethics and palliative care

Part 1 of the updated set of guidelines was recently published. This first part addressed the first 4 areas of SMA care.

This document is quite detailed with references to other key manuscripts in SMA care. Highlights of the updated guidelines include:

1. Both SMN1 and SMN2 copy number should be assessed if there is clinical suspicion for SMA
2. A multidisciplinary approach was identified as a key element in the management of SMA patients
3. Physical assessments including a focused evaluation of the musculoskeletal system should be performed every 6 months
4. Regular sessions of physical therapy are needed with specific goals based on the type of SMA and current clinical presentation of the patient
5. Prolonged cast immobilization (>4 weeks) for long bone fractures should be avoided
6. Nutrition discussions and interventions should include those targeting swallowing dysfunction/dysphagia, weight control, and gastrointestinal dysfunction. These topics as well as growth issues are best evaluated/discussed by a dietician and tailored based on the patient’s SMA type and current clinical presentation.

**Dr. Ramos-Platt’s Comments:** The updated SMA SOC document is timely given the emerging publications of the results of landmark studies in the field. The full document can be found in the February 2018 issue of Neuromuscular Disorders.

**Dr. Rosenfield's Summary and Comments:** Mercuri et al (New Eng. J. Med., 378:625-35; 2018) extended clinical trials of Nusinersen beyond the previously established 2 to 6 months of age in patients: they treated young children with an average age of 3 years. Mercuri et al (Neuromuscular Disorders; 28: 103-115; 2018) review the “Diagnosis and Management of SMA, part 1” with data on how to treat these patients and possible side effects.

Submitted by Nandita S. Keole, MD

The aim of this study was to describe, by a case control and cross-sectional design, the correlation between clinical impairment and age in Charcot-Marie-Tooth type 1A (CMT1A) patients.

Seventy CMT1A patients and 70 sex- and age-matched healthy controls were enrolled. Motor performance was assessed through the 10-m walk test, the 6-minute walk test and the 9-hole peg test of the dominant and non-dominant side, and muscle strength was measured by using the Medical Research Council score. In the CMT1A group, disability and quality of life were evaluated using the Charcot-Marie-Tooth Neuropathy Score (CMTNS) and the Short Form 36 (SF-36) questionnaire. Cross-sectional relationships between age and all clinical measures were analyzed and differences in the slopes between cases and controls were calculated. The occurrence of a structural change in the age-related progression of clinical measures was explored.

The deterioration of motor performance correlated with age in both groups with a greater slope in CMT1A patients than controls. The deterioration of CMTNS and SF-36 correlated with age in the CMT1A group. The deterioration of all clinical measures with the exception of the SF-36 questionnaire showed a structural change at the 50th year of age. The rate of deterioration was no different between patients and controls until 50 years of age, where it became significantly greater in CMT1A patients.

This study supports that the disease progression in CMT1A patients is an age-related process and occurs mainly in the 50th year of age. The loss of strength is more than in control population of the same age.

**Comment:** I believe this article was helpful because we can try to assist patients in preserving motor strength and help further studies to determine which exercise strategies and rehabilitation could help these patients preserve motor strength and function longer.
In this study, the investigators sought to determine the effect of the fascia penetration of the radial nerve in its sensory nerve action potential amplitude. After its origin, the superficial radial nerve courses under the brachioradialis muscle and around the distal to mid-forearm, it pierces the fascia of the muscle and runs in the subcutaneous tissue. The investigators used ultrasound to localize the point of penetration (PP) of the fascia in 83 healthy subjects. The mean PP distance from the styloid process was 8.3 cm (range 5-13). In 20% the PP was less than 7 cms from the styloid process. Nerve conduction studies of the superficial radial nerve were obtained in 25 healthy volunteers with supramaximal stimulation at 5 points (at the PP, 2 and 4 cm proximal to the PP, 2 and 4 cm distal to the PP). The highest amplitude was 2 cm distal to the PP (mean 50.1 mv). The lowest were 2 and 4 cm proximal to the PP (mean 38.1 and 29.7).

Comment: This study highlights the importance of being familiar with the anatomy of commonly tested peripheral nerves. The standard 10 cm distance for stimulation aligns closely with the 2 cm distal to PP point as there are approximately 3 cms between the styloid process and the recording electrode. Because 20% of patients can have the PP at less than 7 cms from the styloid process, it is reasonable to stimulate more distally if the amplitude appears small. It remains unclear if there is any utility of ultrasound for obtaining the largest possible amplitude.
June 13, 2018


Submitted by Niranjan N. Singh, MD

In this issue of *JAMA Neurology,* O’Brien et al present a case-control family aggregation study of genetic pleiotropy within amyotrophic lateral sclerosis (ALS) kindreds. Patients and controls were interviewed and asked about first-degree and second-degree relatives with schizophrenia, bipolar disorder, autism, suicide, obsessive-compulsive disorder, addiction, and alcoholism using definitions from the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition. They collected survey data on 2,116 relatives of patients with ALS and 2,139 relatives of control participants. Confirming results of the previous study, they identified a relative risk of 3.4 (*P* = .02) for developing schizophrenia or other psychotic disorders in relatives of patients with ALS compared with controls. There was also an association between ALS and the development of autism (relative risk, 10.1; *P* = .03), alcoholism (relative risk, 1.48; *P* = .045), and obsessive-compulsive disorder (relative risk, 5.6; *P* = .02). Clustering of psychiatric disease with 3 or more affected family members was higher in the ALS kindreds than the control kindreds. The *C9orf72* mutation did not fully explain these findings, as only 17% of the 29 kindreds with 3 or more affected relatives had the expansion; 81% did not have the expansion.

**Comment:** ALS is a progressive neurodegenerative condition primarily involving the motor system. There is increasing epidemiologic evidence of an association between ALS and a wider spectrum of neurodegenerative and neuropsychiatric disorders among family members, including schizophrenia and psychotic illness and suicidal behavior. The data presented is very suggestive of an association between these diseases and may offer insight into new therapeutic options, but further study is needed before we can conclude that there is any definitive association between them.
June 20, 2018


Submitted by Lisa M. Williams, MD

To date, conflicting theories behind the initial pathogenic mechanism of carpal tunnel syndrome (CTS) exist. Currently, the leading views are inflammatory, resulting from compression of the median nerve and non-inflammatory, fibrosis of the subsynovial connective tissue (SSCT). More recently, researchers have investigated the transverse plane movement of the median nerve as a potential mechanism for CTS. The transverse movement of the median nerve is thought to be reduced with wrist and finger movement in CTS. Using ultrasonography, the researchers of this study designed a cross-sectional, case-controlled study measuring deformation and displacement of the median nerve as it related to severity of CTS confirmed by electrophysiological studies.

Stage 3, moderate to severe CTS confirmed by neurophysiologic studies showed a significantly lower normalized maximal change value of the median nerve movement in response to finger and wrist motions compared with CTS patients in stages 0, 1, and 2 (P <.001).

Comment: The maximum change of median nerve movement may be associated with a degree of fibrosis of connective tissue (ie SSCT) and may be a useful diagnostic ultrasound finding for determination of early onset CTS.
Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive motor neuron disease affecting both the upper and lower motor neurons. It was found that in ALS, blood neurofilament light chain (NfL) levels are elevated. The mechanism and diagnostic values of this finding have been elusive. NfL and phosphorylated neurofilament heavy chain (pNfH) have been found to be elevated in CSF samples of ALS patients compared to the ALS mimics and healthy controls.

This Belgian research group previously showed there is correlation of the CSF NfL level with the serum level. In this article, they did the study based on a cohort of 149 serum samples of patients with ALS, 19 serum samples of patients with a disease mimicking ALS and 82 serum samples of disease control patients. The serum NfL levels were correlated with the number of regions (thoracic, bulbar, upper limb and lower limb) displaying upper and/or lower motor neuron degeneration. The prognostic performances of serum NfL were investigated based on a Cox regression analysis. They showed that serum NfL was associated with motor neuron degeneration driven by upper motor neuron degeneration and was independently associated with survival in patients with ALS.

**Comment:** ALS is the most common motor neuron disease and the diagnosis is still based on clinical history and neurological examination as well as ruling out other ALS mimics. EMG/NCS is the diagnostic test that assesses the denervation in the lower motor neurons. There are no existing validated biomarkers for upper motor neuron dysfunction. On average, there is a 10-12 months delay in diagnosing ALS after the first onset of ALS symptoms. An early and timely diagnosis is desirable both for initiation of therapy and also for the clinical trial enrollment. This work showed that elevated serum NfL levels in ALS are driven by UMN degeneration and the disease progression rate and are independently associated with survival at time of diagnosis. It’s worth noting that elevated CSF and serum NfL have been shown in other neurodegenerative diseases such as Alzheimer’s disease, Huntington’s disease, and frontal temporal dementia, thus making this biomarker less specific. Nevertheless, this study provided a potentially useful biomarker for ALS diagnosis and research.
August 8, 2018


Submitted by John C. Kincaid, MD
Edited by Benn E. Smith, MD

The paper reports about elevated CSF levels of chitinase proteins which are biomarkers of macrophage activation. Elevation of CSF levels of these proteins also correlate with CSF level of a neurofilament protein pNFH which is a marker of axonal degeneration. The degree of elevation correlated with the rate of disease progression. Immune activation has been considered a potential contributor to the pathogenesis of ALS for many years. Two of the 3 proteins studies did not showed elevated levels in patients with primary lateral sclerosis. Unanswered questions include whether macrophage activation influences disease progression/survival independent of the primary degenerative process.
The investigators in this study sought to describe the EMG findings in the rectus abdominis (RA) muscles in patients with clinically definite ALS by El Escorial criteria to see if this could be a suitable muscle to evaluate for denervation of the thoracic region (and thus be an alternative way to evaluate for the third denervated region). Ninety-five consecutive patients were recruited over 5 years. The thoracic paraspinal and RA muscles were sampled at the level of T9. Active denervation was seen in the thoracic paraspinal muscles in 75 patients (79%) and in the RA in 62 (65.3%). Nineteen patients had thoracic paraspinal and not RA denervation. Six patients had RA and thoracic paraspinal denervation. Denervation in RA was more common in older patients.

Comment: RA sampling could be an alternative for evaluation of thoracic region denervation in ALS. Though the RA seems to be less commonly involved than the thoracic paraspinals, it is more easily accessible and easier to relax but there is a risk of peritoneum puncture. The significance of the more frequent denervation of the RA in older patients needs further investigation.
Dysferlinopathies are a group of autosomal recessive diseases that occur when there is decreased or absent expression of the DYSF gene product dysferlin.

Under normal conditions, this protein is involved in membrane repair, and its absence results in muscle fiber necrosis, culminating in replacement of muscle tissue with fat and fibrosis as well as clinical weakness. Dysferlinopathies usually manifest in young adulthood with increased CK and progressive weakness that rarely affects respiratory or cardiac muscle. The most common forms are limb girdle dystrophy 2B and Miyoshi myopathy.

The authors of this research paper sought to describe the pattern and natural history of muscle involvement in said diseases via MRI studies in 185 patients with confirmed mutations. Sequences involved T1, Dixon, B1 Maps and T2, analyzed via T1 Fischer modified Mercuri visual scales.

Quite notably, they describe a characteristic pattern of muscle involvement in dysferlinopathies, independent of clinical phenotype and distinct from other entities such as Becker muscular dystrophy or sarcoglycanopathies.

Dysferlinopathies show fat replacement early on in posterior lower limb muscles (gastrocnemius and soleus) as well as posterior thigh muscles (semimembranosus, semitendinosus and adductor major), pelvic muscles (tensor fascia lata and obturator externus), paraspinals (iliocostalis, multifidus) and scapular muscles (subscapularis, latisimus dorsi) with latter involvement of other muscle groups (levator scapulae, rhomboideus, glutei and gracilis).

Comment: This study is of interest to clinicians, as certain genetic diseases may be suspected via imaging findings.
Eculizumab is an anti-C5 humanized monoclonal antibody. Misawa et al report on a 34 patient, 24-week double-blind, randomized phase 2 study comparing IVIG and 4 weeks of eculizumab (900 mg per dose) versus IVIG and 4 weeks of placebo. The study took place in 13 hospitals in Japan between August 10, 2015, and April 21, 2016.

The dose of a single course of IVIG was 400 mg/kg/day x 5 days. The first dose of eculizumab was given before the course of steroids. Patients were randomized in a 2:1 nature (23 patients received eculizumab and 11 patients received placebo).

The reason for the study was the observation that there is a significant proportion of patients with Guillain-Barré syndrome (GBS) who have significant chronic impairment after treatment. There have been studies demonstrating the role of the complement system in GBS. The efficacy endpoint was proportion of patients that could walk 5 meters independently by week 4. Safety was a second measure. In the treatment group, at 4 weeks, 61% were able to ambulate independently (90% CI 42-78) vs 45% in the placebo group (CI 20-73). One patient in the eculizumab group had an anaphylactic reaction and a second had a brain hemorrhage with subsequent development of an abscess in the area of hemorrhage. One patient in the placebo group developed depression. The authors concluded that because of the lower bound of the CI in the treatment group, the primary outcome measure did not reach the predefined response rate and suggested the need for a larger study.

**Comment:** Monoclonal antibodies against the complement system have demonstrated to be helpful in other autoimmune disorders. One of these disorders is a neuromuscular disorder, refractory myasthenia gravis. The authors have a valid point that the above study is relatively small. In comparison, the REGAIN study evaluating the effectiveness of eculizumab for refractory myasthenia gravis had 4 times as many patients.
In this study, DeLorenzo et al asked the question whether there were features which set anti-PM/Scl autoantibody positive myositis patients apart from those patients with the 3 most common myositis (Dermatomyositis – DM, Antisynthetase Syndrome – AS, and Immune Mediated Necrotizing Myopathy – IMNM). Using data from the John Hopkins Myositis Center Longitudinal Cohort collected between 2002 and 2016, various clinical and diagnostic study parameters found that there were differences which set anti-PM/Scl autoantibody myositis patients apart.

This study stemmed from the observation that myositis overlaps with other connective tissue disorders. Systemic sclerosis is the most common (40%). Out of 949 patients identified as myositis patients in the Myositis Cohort study, 178 had DM, 132 had AS, 185 had IMNM, and 41 were positive for anti-PM/Scl.

Key Features that Set Anti-PM/Scl Patients Apart

1. Muscle weakness was not as prominent early in the course but became more prominent with time
2. Unlike the 3 most common myositis types, the deltoid was more affected than the hip flexors. In DM, AS, and IMNM, the hip flexors were more affected.
3. 23% of patients with anti-PM/Scl positive myositis had distal weakness despite the majority not having clinical generalized scleroderma.
4. Of the 21/41 patients with available muscle biopsy results, 17 had perivascular inflammation.
5. Perifascicular atrophy was twice as common in DM and AS (56% and 52% respectively) compared to 24% in patients with anti-PM/Scl positive myositis patients’ muscle biopsies.
6. Thigh muscle edema seen on MRI was more common in DM, AS, and IMNM, compared to anti-PM/Scl patients (71%, 76%, and 90% respectively vs 39%).
7. Anti-PM/Scl positive patients were more likely to develop pulmonary hypertension (12%) compared to 3% or less in the other 3 disorders.
8. Patients with anti-PM/Scl were more likely to have or develop skin features such as Gottron rashes, mechanic’s hands, sclerodactyly, Raynaud phenomenon, and telangiectasias.
9. Patients with anti-PM/Scl antibody positive myositis tended to respond to immunosuppressive therapies quite well.

Comment: The findings of this study suggest that there are multiple features which set anti-PM/Scl antibody positive myositis apart from DM, AS, and IMNM. This distinction is important when determining overall treatment strategies.
This is the written manuscript by Allen and colleagues (an international cohort of peripheral nerve experts) on IVIg therapy utilization immune-mediated peripheral neuropathy. This review is based on a symposium presented at the 2017 Peripheral Nerve Society meeting in Sitges, Spain. The review is well-structured, beginning with a clear presentation of IVIg immunology, biology and pharmacokinetics, followed by a cogent discussion of the well-known “wearing off” phenomenon and the finally a recommended algorithm to be used to adjust frequency and dose adjustments in individual patients with neuropathies for which IVIg is given.

Comment: This practical review will be of keen interest to all in the readership of *Muscle & Nerve* who use IVIg for immune neuropathies.
In the May 2018 issue of *Journal of Neuromuscular Diseases*, Payam Mohassel and Andrew Mammen from NIH present a timely review of Anti-HMGCR Myopathy.

The review surveys multiple aspects of the disorder:

1. Historical context
2. Clinicopathologic spectrum
3. Anti-HMGCR autoantibody testing
4. Treatment
5. Pathophysiology and mechanism of disease

**Comment:** This paper provides a succinct overview of anti-HMGCR myopathy, a readily diagnosable autoimmune necrotizing myopathy which can mimic LGMD. Although the vast majority have a history of statin exposure a number are statin-naïve. This publication will be useful to those caring for myopathy patients.
Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder that affects 1:3500-1:5000 boys stemming from a pathogenic mutation in the dystrophin gene. Most cases are associated with exon deletions that interrupt the reading frame.

Eteplirsen is an intervention which was designed to restore the reading frame in mature mRNA for certain exon deletion mutations. These mutations are those who are amenable to exon 51 skipping.

Charleston et al report on the results of Sarepta’s study 202, an observational, open-label extension of study 201. Study 201 was the randomized controlled study looking at the efficacy and safety of Eteplirsen in DMD boys with exon 51 skip amenable mutations.

The question raised by the authors was whether 4 different assays on muscle biopsies taken from Study 202 subjects could support the effects of Eteplirsen's ability to skip exon 51 and thus result in increased dystrophin production after 180 days of therapy. 12 patients were included in the study. The assays used were RT-PCR, Western Blot, percent dystrophin positive fibers (immunohistochemical staining for dystrophin, PDPF), and immunofluorescence intensity (Bioquant).

11/12 patients consented to a biopsy on study week 180. On RT-PCR, all 12 patients confirmed positive exon skipping and 9/11 available biopsies demonstrated an increase of dystrophin. In Western blot (measured as % normal), Bioquant, and PDPF means were 0.93 vs 0.37, 22.61 vs 9.41, and 37.33 vs 5.04 respectively.

Comment: In September 2016, Eteplirsen received accelerated FDA approval for the treatment of DMD patients with exon 51 skip amenable mutations. While questions remain regarding whether increased dystrophin expression results in increased strength, this study does demonstrate that Eteplirsen increases dystrophin production. There is a subset of Duchenne patients who spontaneously skip exons resulting in small amounts of dystrophin. These patients (exon 44 skip amenable patients) tend to have a milder disorder. It would be important to follow the boys in Study 202 over time to assess if they follow the same trajectory as the subpopulation of Duchenne patients who spontaneously skip.
Making mention that the majority of journal articles are focused on male patients with dystrophinopathy, Ishizaki and colleagues review the manifestations in female carriers. The effect of dystrophin abnormalities in female carriers spans the clinical spectrum. Ishizaki pulled together an impressive compilation of data from the literature solely devoted to female dystrophinopathy including articles focused on epidemiology, clinical symptoms, cardiomyopathy, burdens on parents or caregivers, pregnancy or delivery, and prognosis.

**Comment:** Those who care for muscular dystrophy patients will find this a valuable resource as they continue to care for not only the more common population of boys and young men with Duchenne muscular dystrophy but also for their sisters, mothers, and other female relatives. Reviewing 1,002 papers on this subject, they collect and present data on 93 manifesting patients, emphasizing that this remains an area for further research.
Ultrasound nerve cross sectional areas were carefully measured unilaterally in 100 normal volunteers. The goal was to improve ultrasound diagnosis of peripheral neuropathy by setting cutoff values for the UPSS, a summation score for nerve enlargement. Patients with a history of neuromuscular disorders, diabetes, or use of neurotoxic medications were excluded, and all had a normal neurologic exam. The median nerve was evaluated at four locations, ulnar at three, the superficial radial, tibial, and peroneal at two locations, the sural and vagus nerves, C5 and C6 nerve roots at one location. Data was analyzed by gender, age, height and weight.

There were relatively few significant differences. Males had significantly larger cross sectional area in the proximal and distal tibial nerve (8 and 13%), and the proximal median nerve (7%). Areas of the distal median nerve and the proximal tibial nerve increased significantly with age. Only the cross sectional area of the tibial nerve increased with height. No nerves showed significant correlation with weight. Most values were similar to previous studies. More gender related differences had been observed in some previous studies.

Overall, median and tibial nerve cross sectional areas must be adjusted for age and gender. The tibial nerve cross sectional area should also be adjusted for height.

Comment: Overall this was a well-designed study of the ultrasound cross sectional area of many commonly evaluated nerves in a normal population, analyzed by gender, height, weight and age. There were surprisingly few significant differences. Of note, while there was a large age range in this study, height and weight showed modest variation (80% of subjects were 60-90 Kg). It is not clear whether these values would apply for unusually short, tall, thin, or heavy patients. The data from this study can be used to improve diagnosis of peripheral neuropathies.
Ulnar mono-neuropathy is non-localizable (NL-UN) when there is clinical ulnar neuropathy, reduced ulnar distal sensory and/or motor amplitude, but no focal slowing or focal loss of amplitude. This study investigated the frequency and severity (clinical and electrophysiologic) of NL-UN, and whether ultrasound of the nerve could assist in the diagnosis of NL-UN. One hundred thirteen patients referred for electrodiagnostic testing with signs and symptoms of ulnar neuropathy had electrodiagnostic testing. Sixty-four patients had reduced ulnar distal motor or sensory amplitude, 48 localizable (75%) and 16 (25%) non-localizable. The NL-UN patients were predominately male, had significantly more severe clinical findings and greater amplitude reduction than the localizable patients.

All NL-UN patients received ultrasound scanning of the ulnar nerve from the wrist to mid humerus. The ulnar diameter was measured at the widest area, and compared with normal values. All ultrasound studies were abnormal. Most of the patients (13/16, 81%) had evidence of focal enlargement at the elbow. The other 3 (19%) had evidence of diffuse ulnar enlargement. All 3 were diabetic, indicating probable diabetic neuropathy.

Comment: There is a fairly high incidence of NL-UN. Previous studies have shown some variation in incidence. All patients with NL-UN showed ulnar pathology on ultrasound, some quite severe, most with focal ulnar enlargement across the elbow. This strongly suggests that ultrasound evaluation should be considered in any case of non-localizable ulnar neuropathy.