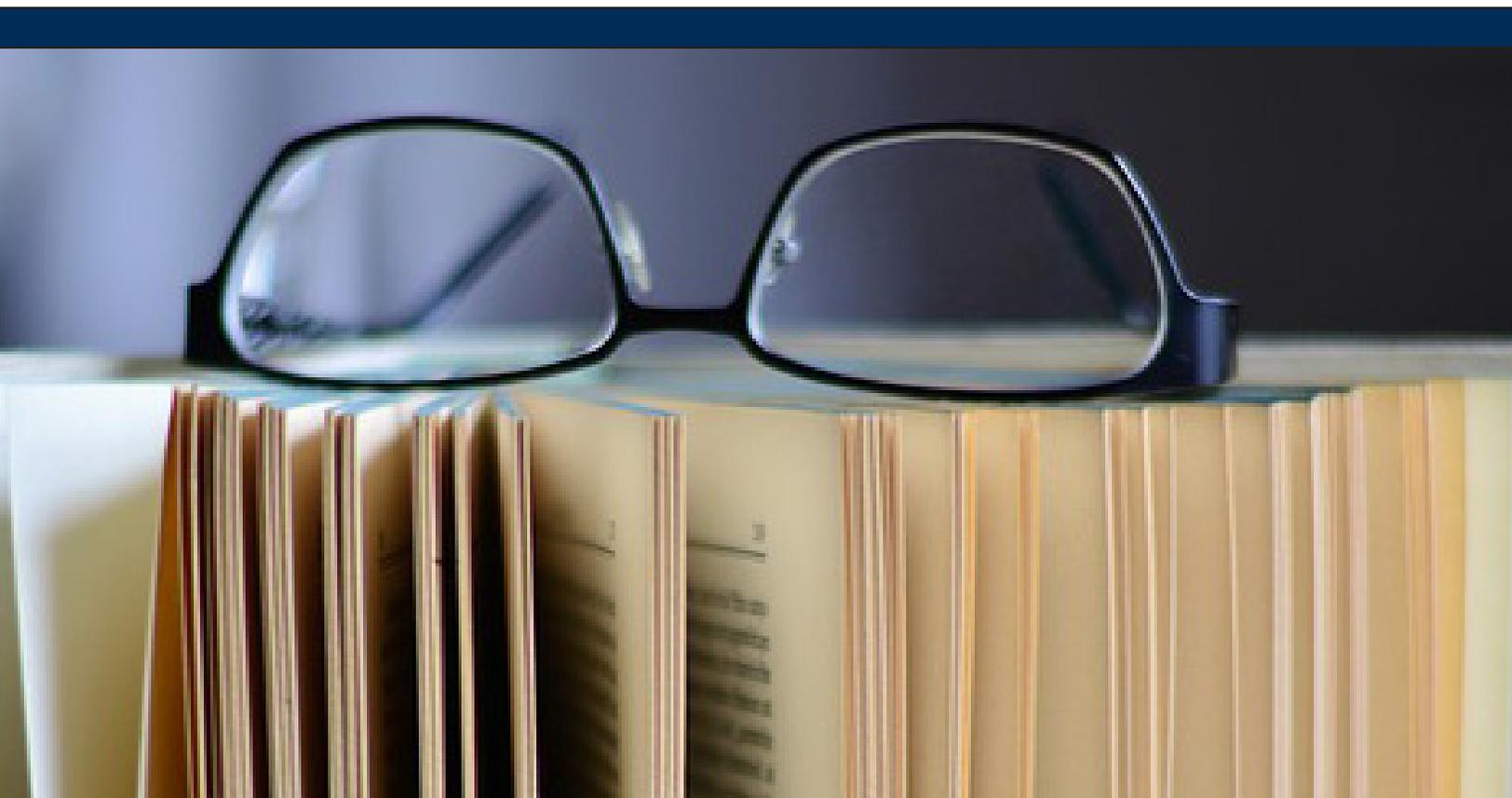
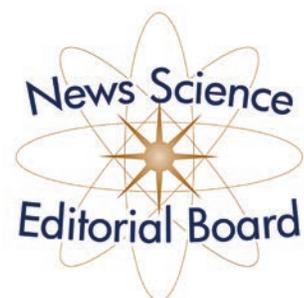


News Science Anthology

January 2019 - December 2019



Articles on NM and EDX medicine selected by the
AANEM News Science Editorial Board



Anthology of NSEB Journal Article Summaries and Comments January 2019 - December 2019

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January 4, 2019

Wolpaw JR, Bedlack RS, Reda DJ, et al. **Independent Home Use of a Brain-Computer Interface by People with Amyotrophic Lateral Sclerosis.** *Neurology* 2018;91:e258-e267.

Submitted by: Bryan DeSouza, MD

Edited by: Rocío Carolina García Santibáñez, MD

Wolpaw et al. report the first prospective, multi-site, clinical trial of a Brain Computer Interface (BCI) to restore communication in patients with ALS.

In this study, Wolpaw and colleagues assessed the reliability and usefulness of the Wadsworth BCI system, an EEG–scalp recorded BCI, as a practical communication device in advanced ALS patients in a home environment for up to 18 months. BCI use included audio books, conversation, copy-spelling/calibration, email, internet newsreader, pictures and YouTube. Outcome measures were extent and nature of BCI use, BCI benefit versus burden, quality of life, technical support and patient attrition.

The study recruited 42 veterans with loss of verbal and/or written communication on the ALSFRS-R (ALS Functional Rating Scale-Revised), but preserved reading and understanding. Of these patients, 28 were able to participate in the study, their caregivers were trained and they had use of the BCI in their homes. 9 patients (21%) dropped out due to death or disease progression, 4 lost interest, and 1 was lost to follow-up. The remaining 14 patients used the BCI for 2-17 months mainly for communication. Technical problems were rare. Patient and caregiver ratings showed BCI benefit surpassed burden. McGill Quality of Life assessments were stable despite disease progression. At the end of the study, 7 of 8 participants chose to keep the BCI for further use indicating that patients felt it was important and useful for communication.

This clinical trial shows that the EEG-based brain computer interface (BCI) operated independently by patients with ALS is a useful and reliable tool for communication in a home setting with proper training and minimal support.

Comment: The study is important because it establishes proof of concept that a non-invasive BCI device can improve communication and potentially motor control in a practical way. As technology improves, so will the speed, efficiency, applications and number of the devices that will be available for our patients. Moving forward, it will be important for physicians involved in treating and managing neuromuscular diseases and neurorehabilitation to understand the uses and limitations of this technology.

January 10, 2019

Doneddu PE, Cocito D, Manganelli F, et al. **Atypical CIDP: Diagnostic Criteria, Progression and Treatment Response. Data from the Italian CIDP Database.** *J Neurol Neurosurg Psychiatry*. Published Online First: 08 October 2018. doi: 10.1136/jnnp-2018-318714.

Submitted by: Francisco E. Gomez, MD

Edited by: Niranjan N. Singh, MD

In this multi-center retrospective analysis, the authors sought to describe several variants of atypical CIDP as well as their respective diagnostic criteria. These variants are well characterized in the text and include Distal Acquired Demyelinating Syndrome (DADS), pure motor or pure sensory CIDP, Lewis-Sumner Syndrome (MADSAM; Multifocal acquired demyelinating sensory and motor neuropathy) and Focal CIDP. They then applied said diagnostic criteria to a pool of 460 patients (median age 60, 64% men), finding 82% of cases diagnosable as typical CIDP and 18% as atypical (34 DADS, 17 Motor CIDP, 16 sensory CIDP, and 17 with Lewis-Sumner Syndrome). Of interest, they later found that 39% of patients at initial presentation met atypical CIDP criteria, of which 53% progressed to typical CIDP by 5.5 years. Typical CIDP tended to be more disabling. A large proportion of the atypical subtypes of CIDP were treatment responsive.

Comment: In this large retrospective review article from a pool of 460 patients, authors have tried to analyze the clinical features and phenotype of typical and atypical CIDP, prognosis and treatment response. Of 1 in 5 patients diagnosed with atypical CIDP at the onset, more than 50% progress to typical CIDP over a span of more than 5 years. DADS and LSS have a less frequent response to intravenous immunoglobulin compared to typical CIDP, raising the possibility of a different underlying pathogenetic mechanism.

January 16, 2019

Wagner FB, et al. **Targeted Neurotechnology Restores Walking in Humans With Spinal Cord Injury.** *Nature* 2018;563; 65–71.

Submitted by: Hristelina Ilieva, MD, PhD

Edited by: Niranjana N. Singh, MD

The authors report a novel, targeted, spatio-temporal spinal cord stimulation in 3 patients with chronic spinal cord injuries (4 years post trauma) who had permanent motor deficits or complete paralysis despite extensive physical therapy. The authors mapped carefully in each of the 3 patients the pools of different lumbo-sacral motor neurons (those controlling hip flexion, ankle extension, etc.) and placed 16 electrode paddle array over the respective dorsal roots. Then they delivered via wireless communication epidural electrical stimulation (EES) in real-time, spatially selective (i.e. stimulating first hip flexors, then ankle extensors, etc) trains that coincided with intended movement. Within a week that led to establishing an adaptive control over the paralyzed muscles. The paradigm included 5 months of physical therapy including overground assisted walking. Locomotor performance improved during rehabilitation. Patients progressed from stepping on a treadmill to supported walking on the ground (while receiving EES), and were able to adjust their step elevation and stride length. Over time, patients could walk for up to 1 hour on the treadmill with EES. Following rehabilitation, the 3 patients could walk independently (either partially supported or with a walker) with EES, and regained voluntary leg movements without EES.

In an accompanying paper published in *Nature Neuroscience*, the same group reports the importance of using burst stimulation and spatiotemporal stimulation profiles versus continuous stimulation to be able to preserve proprioception stimulation. In continuous stimulation, the proprioceptive inputs get cancelled reducing or abolishing the conscious perception of leg position, which limits the success of the rehabilitation.

Comment: This is a breakthrough discovery which sets the stage for trials with a large patient population with varying degrees of trauma (complete versus partial spinal cord transection injuries). Experience in more laboratories will help confirm the initial observations and bring those discoveries to a wider range of patients. It will be interesting to see if cervical spinal cord injuries are amenable to a similar approach and if earlier initiation (before 4 years) offers better chances for a more complete recovery. These results establish a technological framework for improving neurological recovery and supporting the activities of daily living after spinal cord injury.

January 23, 2019

Wu YT, Ke MJ, Ho TY, et al. **Randomized Double-blinded Clinical Trial of 5% Dextrose Versus Triamcinolone Injection for Carpal Tunnel Syndrome Patients.** *Annals of Neurology.* 2018;84(4):601-610

Submitted by: Clark W. Pinyan, MD, MPH

Edited by: Niranjan N. Singh, MD

In this study, the authors compared injection of 5cc D5W (dextrose group, 27 wrists) to 3ml triamcinolone in 2cc NS (steroid group, 27 wrists) under ultrasound guidance in patients with mild to moderate carpal tunnel syndrome. Both groups showed improvement in both the visual analog scale of symptoms and the Boston Carpal Tunnel Questionnaire in the first 3 months. Improvement in the steroid group reversed through the 3rd to the 6th month, with continued improvement in the dextrose group. Significant difference between the 2 groups was seen at the 4th and 6th months. Electrophysiologic measures were also compared. Ultrasonographic median nerve cross sectional area decreased in both groups over 6 months, and sensory nerve conduction velocity decreased in the dextrose group. Overall, however, there were no noteworthy differences between electrophysiological findings in the steroid and dextrose groups. The authors conclude that a single perineural D5W injection leads to significant reduction in pain and disability compared to the corticosteroid, from the 4th month post injection, and given the side effects of steroids, deem it to be a “better choice.”

Comment: This is a small but prospective double-blind randomized trial comparing the efficacy of ultrasound-guided steroid versus dextrose injection in mild to moderate carpal tunnel syndrome. Steroid injections have been used for decades in mild to moderate carpal tunnel syndrome – major drawbacks being short-term benefit and neurotoxicity. Dextrose injections are emerging as a novel therapy with longer duration of benefit in mild to moderate carpal tunnel syndrome.

January 31, 2019

Fulii T, Yamasaki R, Iinuma K, et al. **A Novel Autoantibody Against Plexin D1 in Patients With Neuropathic Pain.** *Annals of Neurology.* 2018;84(2):208-224.

Submitted by: Clark Pinyan, MD, MPH

Edited by: Bryan DeSouza, MD

The authors actively sought novel autoantibodies in patients with neuropathic pain. Among 110 patients with neuropathic pain tested by tissue based IFA, 11 patients had a characteristic pattern of binding to mouse unmyelinated C-fiber type dorsal root ganglion (DRG) neurons. Mass spectrometry analysis of the immunoprecipitant yielded a partial sequence identical to plexin D1 amino acids. Most of these patients had other identified immune conditions including Sjogren's syndrome, asthma, and allergic rhinitis. The majority were young (26.3 ± 13.3), female (81.8%) and had relapsing or fluctuating clinical courses (100%). Seven patients underwent immunotherapy for related conditions, and all 7 reported improvement in neuropathic pain.

Comment: This paper is an important first step in identifying biomarkers for neuropathic pain in a cohort of Japanese patients. 10% of the neuropathic pain patients were found to have anti-unmyelinated C-fiber type DRG neuronal antibodies directed against the plexin D1 antigen. Although this is an important finding, the majority – 90% of the neuropathic patients screened – did not have these autoantibodies. A majority were candidates for immunotherapy based on other systemic diagnoses (most commonly Sjogren's syndrome), and all noted improvement in pain with treatment. This article highlights the growing importance of autoantibodies in neuropathic processes including pain.

February 7, 2019

Jin P, Cheng L, Chen M, Zhou L. **Low Sensitivity of Skin Biopsy in Diagnosing Small Fiber Neuropathy in Chinese Americans.** *Journal of Clinical Neuromuscular Disease.* 2018;20:1-6.

Submitted by: T. Darrell Thomas, MD

Edited by: Bryan DeSouza, MD

Small fiber sensory neuropathy (SFSN) is a common entity seen in the NM clinic. Most often it is associated with diabetes but can be seen with a multitude of other conditions including other medical conditions, toxins, hereditary and immune mediated conditions. Many times patients are frustrated knowing they have neuropathic symptomatology but conventional EDX techniques are unrevealing. Frequently patients request confirmation of the diagnosis, and skin biopsy for intraepidermal nerve fiber density (IENFD) measurements is performed. In this article by Jin and associates, they described that nominative values for diagnosing SFSN differs in Chinese Americans versus other ethnic groups. In this study, a total of 23 Chinese Americans and 32 non-Chinese Americans were studied for the presence of small fiber neuropathy. The diagnostic sensitivity for IENFD was significantly lower in Chinese Americans (26.1%) compared to non-Chinese Americans (62.5%, $p=0.01$). IENFD was found to be significantly higher in Chinese Americans versus non-Chinese Americans. This has previously been reported in a healthy Thai population. They conclude that current nominative IENFD is influenced by ethnic differences in addition to sex and age.

Comment: This article adds additional insight in the evaluation of non-Caucasian patients with the diagnosis of small fiber neuropathy. When seeing a patient of different ethnicity, one must take into consideration that even if the test is normal, the patient can still have SFSN. This study is somewhat faulted in that the non-Chinese Americans included 78% Caucasian but other ethnic groups were included. It is possible that the diagnostic sensitivity in a pure Caucasian cohort would have been higher than 62.5%.

February 14, 2019

Yurie H, Ikeguchi R, Ohta S, Oda H, Takeuchi H, Matsuda S. **Peripheral Nerve Regeneration Using a Bio 3D Conduit from Undifferentiated Bone Marrow Stromal Cells.** *The Journal of Hand Surgery.* 2018. doi: 10.1016/j.jhssa.2018.06.074

Submitted by: Lisa M. Williams, MD

Edited by: Bryan DeSouza, MD

The reference standard for nerve regeneration includes use of autologous nerve grafting. However, biocompatibility is low and risk of infection is a concern. To address this issue, a 3D biologic conduit using undifferentiated bone marrow stromal cells (uBMSCs) to promote peripheral nerve regeneration in peripheral nerve injuries involving a nerve gap were studied. Efficacy of this new technique was compared to previously studied fibroblast conduits.

In this study, primary uBMSCs were isolated from femoral bone marrow of Lewis rats. Fibroblasts were harvested from subcutaneous skin tissue. Conduits were made from both cells using a bio 3D printer and interposed onto rat sciatic nerves spanning a 5mm nerve gap. Electrophysiologic studies showed significantly higher compound muscle action potential (CMAP) amplitude ($p < .05$) in rat adductor muscles using uBMSCs and a greater amount of myelinating axons were noted in the uBMSC ($p < 0.5$).

Comment: Biologic regeneration techniques targeting peripheral nerve injuries are an emerging area of research. More studies are needed to evaluate the safety and efficacy in humans.

February 21, 2019

Mora A, Blazar PE, Teplitz BA, Rogers J, Economy K, Earp BE. **Prospective Evaluation of the Incidence and Persistence of Gestational Carpal Tunnel Syndrome.** *The Journal of Hand Surgery.* 2018. doi: 10.1016/j.jhsa.2018.06.036.

Submitted by: Lisa M. Williams, MD

Edited by: Bryan DeSouza, MD

Pregnancy is a known risk factor for gestational carpal tunnel syndrome (GCTS), however the incidence is not known. Currently there is no known specific demographic or comorbid conditions associated with the incidence of GCTS.

A study of 420 pregnant patients was conducted in which they completed the Levine-Katz Questionnaire (LKQ) in their third trimester of pregnancy. Symptomatic women in their third trimester were followed up with at 2-6 weeks, 3 months, 6 months and 12 months postpartum. Follow-ups continued in symptomatic women until symptoms resolved or women underwent surgical treatment.

The findings were that 102 women (27.7%) were symptomatic and diagnosed with GCTS during their third trimester. Postpartum follow-up was completed with 65% of the women. 4.6% had escalation of symptoms at one year. Women with and without GCTS were of similar age ranges (32.2-32.9), had higher rates of smoking (28.9% versus 13.3%), higher pre-gravid BMI (28.2 versus 26.1), higher rates of preeclampsia (9.3 versus 2.3%) and similar rates of cardiac disease and diabetes.

Comment: There is a high incidence of GCTS in the third trimester in previously asymptomatic patients and symptoms may persist beyond pregnancy. There are demographic and comorbid conditions associated with the incidence and perseverance of GCTS.

April 4, 2019

Albrecht P, Jansen A, Lee J, Moll M, Ringelstein M, Rosenthal D, Bigalke H, Aktas O, Hartung H, Hefter H. **High Prevalence of Neutralizing Antibodies after Long-term Botulinum Neurotoxin Therapy.** *Neurology* 2019;92:e48-e54.

Submitted by: Bryan X. DeSouza, MD

Edited by: Hristelina Ilieva, MD, PhD

Summary: A single center large observational cross-sectional study of 596 patients was performed by Albrecht et al. to determine the prevalence of neutralizing antibodies (NAbs) against botulinum neurotoxin type A (BoNT/A) in long-term BoNT/A treatment for different neurologic indications including hemifacial spasm, blepharospasm, cervical and other dystonias, as well as spasticity. Their study was designed to analyze the probability of remaining NAb negative with the duration of treatment and identifying factors contributing to the induction of NAbs.

At the Heinrich Heine University Neurology clinic, 596 patients were recruited from 2013-2014. The inclusion criteria was as follows: patients were injected for standard indications of dystonia and spasticity and received 4 Botox injections over 1 year. Testing for NAbs was standardized and blinded for binding antibodies and neutralizing antibodies. Data from this cohort was analyzed to determine effects from indications/anatomical sites in 5 subgroups: facial hemispasm (FHS), blepharospasm (BSP), cervical dystonia (CD), other dystonia types (ODT) and spasticity. The effects of the duration of injection therapy and dose level per injection using unified dose units for the different products [abo-BoNT/A (Dysport), ona-BoNT/A (Botox) and inco-BoNT/A (Xeomin)] were also assessed.

Results: 83 of 596 patients (13.9%) had measurable NAbs. Except for FHS, all other subgroups tested positive for NAbs. Kaplan-Meier analysis was performed, and in all subgroups, the curve declined over time, suggesting a nonlinear increase in conversion to NAb positivity with longer durations of treatment. The curves of the ODT, CD, and spasticity subgroups suggest that patients with these indications and duration of treatment of ≈ 15 years have a risk of up to 30% to 40% to become NAb positive.

The influence of doses on NAb induction was assessed. Their data shows that the probability of developing NAbs increases with the duration of treatment, is dose-dependent, and is significantly higher in patients having received mean doses of >350 uDU

A stepwise regression analysis was performed. The main influence on NAb induction was the BoNT/A formulation followed by single dose per session ($p < 0.01$ and $p = 0.023$, respectively). No additional significant influence was revealed for cumulative lifetime dose, disease entity, or treatment duration.

Comment: Our understanding of the immune system and our ability to manipulate its responses as a therapeutic tool to enhance or suppress immune responses are rapidly evolving. The long term effects of hybridized immunobiologic treatments, reconstitution of the immune system for oncologic therapy and the immunologic responses to medical toxins all have unintended consequences in the neuromuscular system but are poorly understood.

April 11, 2019

Petrini F, et al. **Six-month Assessment of a Hand Prosthesis With Intra-neural Tactile Feedback.**
Annals of Neurology 85(1): 137-154 <https://doi.org/10.1002/ana.25384>

Submitted by: Clark W. Pinyan, MD, MPH

Edited by: Hristelina Ilieva, MD, PhD

Summary: Three trans-radial amputees received implants of transverse, intra-fascicular, multichannel electrodes (TIME) in residual median and ulnar nerves. Electrodes were attached to sensors in the digits of a prosthesis to generate sensory feedback while performing different grasping tasks. All subjects reported stimulation-induced sensations from the phantom hand for the whole duration of the trial. They also successfully integrated the sensory feedback into their motor control strategies while performing experimental tests simulating tasks of real life. Finally, they reported a decrement of their phantom limb pain and a general improvement in mood state.

Comment: Sensory feedback devices are becoming more stable and functional with chronic implantation. This is yet another step in the development of truly integrated prosthetic devices.

May 8, 2019

Kesici, S. et al. **A Novel Treatment Strategy for Severe Guillain-Barre Syndrome: The Zipper Method.** *Journal of Child Neurology* 2019 DOI: 10.1177/0883073819826225.

Submitted by: Leigh Maria Ramos-Platt, MD

Edited by: Hristelina Ilieva, MD, PhD

Summary: Kesici et al describe a novel approach in the treatment of pediatric patients ages 6-16 years of age, with acute motor axonal neuropathy in an open-label study. In their study, 9 patients, who all presented within 2 days of symptom (complaint) onset, were admitted to the intensive care unit because of respiratory failure (required mechanical ventilation), had CSF studies within a day of admission, and were confirmed to have acute motor axonal neuropathy (EMG performed within 4 days of presentation). Not all patients had elevated protein. GM1 antibodies were not performed.

The zipper strategy consists of the following:

Day 1: Treatment with 1.5x plasma exchange with 5% albumin as replacement followed by 0.4 grams/kg of IVIG immediately after

Day 2: After 24 hours, 1x plasma exchange with 5% albumin followed by 0.4 grams/kg of IVIG

Day 3: 1x plasma exchange with fresh-frozen plasma followed by 0.4 grams/kg of IVIG

Day 4: A repeat of day 2

Day 5: A repeat of day 2

This resulted in the following:

1. Mechanical ventilation need of 5-14 days and no permanent tracheostomy placement
2. A hospital stay of 10-30 days
3. All patients were able to walk unassisted by day 28

All of these results are superior to those reported in adult patients (in the medical literature) who received IVIG or plasmapheresis alone.

Comment: The worse outcome patients with acute motor axonal neuropathy (AMAN) were discussed in this article. It is also something we see in practice. This article is interesting as it presents the use of concomitant therapies. In practice, we tend to do sequential treatments rather than concomitant treatments. A larger, multi-center, randomized, controlled with single- either IVIG or PE -treatment group (s) study could help interpret the above findings. The jury is still out if this regimen will be supported in a more robust trial. Because of the rarity of AMAN patients, those trials may be difficult to execute in western countries. The practical use of this protocol in terms of insurance coverage may also be problematic until further proof is collected.

May 21, 2019

Walker F, Cartwright M, Alter K, et al. **Indications for Neuromuscular Ultrasound: Expert Opinion and Review of the Literature.** *Clinical Neurophysiology*, 2018, 129:2658-79.

Submitted by: Elliot Bodofsky, MD

Edited by: Clark W. Pinyan, MD, MPH

Summary: In this study, 19 worldwide experts in clinical neurophysiology (neurologists, physiatrists and neurophysiologists) completed detailed surveys about indications for diagnostic ultrasound (US) for a wide variety of disorders. Over 250 articles were reviewed. For each condition, they were to indicate whether US should be used in some cases, or as the first diagnostic modality.

A majority of the experts used US (in some cases) for all types of focal nerve disorders (e.g. CTS), demyelinating polyneuropathies, ALS, most regional or multifocal nerve disorders (e.g. brachial plexopathy), generalized muscle disorders (e.g. inclusion body myositis), and situational indications, including palpable masses, variant anatomy, young children and phobic patients. Over 25% recommended US as the first diagnostic tool for focal nerve disorders, regional or multifocal nerve disorders (47% for nerve tumors and neuromas), focal muscle disorders (40% for diaphragm paresis), 47% for palpable masses and 67% for phobic patients or young children. The group outlined many ways that US can improve diagnosis. A large majority felt that US helps to demonstrate local anatomy, complements electrodiagnostic findings, and identify unexpected findings. An even larger majority (90%) felt that US will improve over time, more EMG labs will offer US, US will be used more for research, and residencies will include US training. Overall, they believe that NM US is becoming a third component of neurodiagnostic testing, in addition to NCS and EMG.

Comment: NM US can improve diagnosis for many common and important areas of neurodiagnostic medicine, either as the first test, or a secondary test to be used in appropriate cases. The vast majority of world experts see the role of US increasing. More research is needed and residents need NM US training.

May 22, 2019

de Greef BTA, Hoeijmakers JGJ, Geerts M, Oakes M, Church TJE, Waxman SG, Dib-Hajj SD, Faber CG, Merkies ISJ. **Lacosamide in Patients With Nav1.7 Mutations-related Small Fibre Neuropathy: a Randomized Controlled Trial.** *Brain*, Volume 142, Issue 2, 1 February 2019, Pages 263–275.

Submitted by: Francisco E. Gomez, MD

Edited by: Clark W. Pinyan, MD, MPH

Summary: Small fiber neuropathy (SFN) is a condition often encountered in the outpatient setting, preferentially affecting A δ and unmyelinated C fibers. First line treatment for SFN includes tricyclic antidepressants, SSRIs, SNRIs, gabapentin and pregabalin or combinations, which are not always satisfactory.

Voltage gated sodium channels mediate membrane depolarization and are found in dorsal root ganglia neurons. Gain of function mutations in these channels are described in patients with neuropathic pain. Specifically, 15% of SFN cases are associated with mutations in the SCN9 gene coding for NaV1.7. Lacosamide binds to these channels; thus, the authors theorized this antiepileptic may prove effective for SFN.

Authors conducted the Lacosamide Efficacy and Safety in SFN Study, a randomized placebo controlled double blinded crossover study performed in a single center, the Maastricht University Medical Center. A total of 25 patients were randomized to lacosamide versus placebo then crossed over. The primary endpoint was a 1 or more point decrease in self-reported daily pain and improvement in sleep interference scales. Fifty to 60% of patients reported some improvement as defined in the primary outcome measures, more marked in patients with a known NaV1.7 mutation. Patients did not alter their pre-existing medication regimens, so the authors conclude that Lacosamide is a potential add-on medication with few intolerable interactions or side effects.

Comment: Having another effective medication for SFN would be of great interest for clinicians treating this common disease. The limitations to this study are not only its size but also the emphasis on NaV1.7 mutations, which are not tested as routine clinical practice.

June 4, 2019

Wolfe G, Kaminski H, Aban I, Minisman G, Kuo H, Marx A, et al. **Long-term Effect of Thymectomy Plus Prednisone Versus Prednisone Alone in Patients With Non-thymomatous Myasthenia Gravis: 2-year Extension of the MGTX Randomised Trial.** *The Lancet Neurology.* January 25, 2019.

Submitted by: Rocio Carolina Garcia Santibanez, MD

Edited by: Clark W. Pinyan, MD, MPH

Summary: Authors report a 2 year extension of the landmark MGTX trial published in 2016. The objective was to evaluate long term effects of thymectomy in non-thymomatous myasthenia gravis for up to 5 years. Enrolled patients had a diagnosis of generalized myasthenia, aged 18-65 with disease duration of less than 5 years, positive AchR antibodies and no evidence of thymoma. Patients were randomized to trans-sternal thymectomy and prednisone or prednisone only. Of the 111 patients in the initial trial, 68 continued in the extension trial but 50 completed it (33 in the prednisone group and 26 in thymectomy plus prednisone group). As seen in the initial trial, the thymectomy plus prednisone group had lower QMG (quantitative myasthenia gravis) score and lower average alternate day prednisone dose (24mg vs 48mg). Hospitalization for MG exacerbation was more common in the prednisone only group.

Comment: Though this is a smaller cohort than the original study, it appears that thymectomy continues to provide benefits up to year 5 in non-thymomatous generalized myasthenia gravis.

June 17, 2019

Pelosi L, Mulroy E. **Diagnostic Sensitivity of Electrophysiology and Ultrasonography in Ulnar Neuropathies of Different Severity.** *Clinical Neurophysiology*, 2019, 130: 297-302.

Submitted by: Elliot Bodojsky, MD

Edited by: T. Darrell Thomas, MD

Ulnar neuropathy at the elbow is the second most common mononeuropathy. Electrophysiological sensitivity is lower than for carpal tunnel syndrome in a significant portion of cases. Frequently, studies are abnormal but not localizable. Recently nerve ultrasound has been used to evaluate ulnar compression. This study evaluated the accuracy of electrophysiological and ultrasound testing in 135 consecutive patients who were referred with neuropathic symptoms in the ulnar distribution of varying severity. Severity was graded with an established scale of symptoms and physical findings. Electrophysiologic studies were conducted using AANEM guidelines which included inching techniques when results were otherwise not conclusive. EMG of additional ulnar muscles was performed when NCS were non-localizing. Ultrasound testing involved scanning from the wrist to mid-humerus with measurements of cross-sectional nerve area.

Sensitivity was slightly higher for ultrasound (58%) than electrophysiology (47%). The difference was almost exclusively in the clinically very mild group (20% for ultrasound, 3% for electrophysiology) and the clinically mild group (62% vs. 47%). Both techniques had extremely high sensitivity for the clinically moderate and severe groups. A combination of the two techniques resulted in a higher sensitivity. Twenty-five patients with non-localizable EDX abnormalities showed abnormalities on ultrasound testing. There was very strong correlation between clinical and electrophysiological severity scores ($R=0.87$), between maximum ultrasound cross-sectional area and clinical severity ($R=0.78$), and between ultrasound and electrophysiological severity ($R=0.82$).

Comment: This is a study that compared electrophysiological and ultrasound testing for ulnar neuropathy symptoms of different severities. Ultrasound may detect more clinically very mild or mild cases providing evidence when EMG/NCS is abnormal but non-localizing. Clinical, electrophysiological and ultrasound severity are all highly correlated. Accuracy for clinically mild cases is improved when both techniques are used.

July 1, 2019

Restivo D, et al. **Efficacy of Botulinum Toxin A for Treating Cramps in Diabetic Neuropathy.** *Annals of Neurology* 84(5): 674-682

Submitted by: Clark W. Pinyan, MD, MPH

Edited by: T. Darrell Thomas, MD

Summary: Fifty diabetic patients with diabetic neuropathy and cramps were randomly assigned to two groups. BTX-A (30 or 100 units, depending on site) or saline was injected bilaterally into the gastrocnemius or the small flexor foot muscles. Changes in pain intensity and cramp frequency were evaluated over 20 weeks. Treatment was repeated 5 months after first injection in 19 responders. All outcome measures improved significantly after BTX-A compared with placebo. Improvement began at 1 week post injection and persisted up to week 14. Five of 25 (20%) of patients were non responders. Repeat BTX-A injection produced similar results to the initial administration.

Comment: Botulinum toxin injections are already useful in a variety of clinical conditions with cramps and spasms such as multiple sclerosis or lumbar spinal stenosis. This may be an emerging tool in our clinical arsenal in patients who are often refractory to other therapies. This would be contingent on ability to secure reimbursement for these services. Further research may lead to greater acceptance and greater payor approval.

August 28, 2019

Bandres-Ciga S et al. **Shared Polygenic Risk and Causal Inferences in Amyotrophic Lateral Sclerosis.** *Ann Neurol* 2019;85:470-481

Submitted by Clark Pinyan, MD, MPH

Edited by Lisa Williams, MD

Epidemiological studies of ALS can be limited by the sometimes rapid progression of the disease. New methods of risk analysis including genome-wide association studies were reviewed in reference to the recently published ALS-GWAS. Analysis of whole genome data with linkage disequilibrium score regression on over 20,000 (mostly European) ALS patients and 59,000 controls looked at correlations with over 700 phenotypic traits. Positive correlations for ALS were seen with smoking status and moderate physical activity. Negative correlations were seen with higher cognitive performance, higher educational attainment and light physical activity. Secondly, Mendelian randomization suggests a causative relationship between hyperlipidemia and ALS.

Genome linkage studies use genetic markers associated with a risk (such as tendency to smoke, cancer, or hypercholesterolemia), compared with incidence of a particular condition, in this case ALS. This can overcome some limitations of traditional epidemiology such as recall or selection bias, by being independent of patient self-reporting or selection. Furthermore, Mendelian randomization can suggest a causative link if certain conditions are met.

Comments: In this no-hypothesis exploratory study, there is some genetic confirmation of epidemiologically suggested risks for ALS including smoking, lower education and hyperlipidemia, though the traditional epidemiological studies for low-density lipoprotein and ALS are somewhat mixed. The positive correlation with moderate exercise was unexpected and needs further explanation. Use of whole genomic data to determine risk for ALS may be useful in overcoming limitations in epidemiological studies of ALS in both research and clinical practice.

V Iyer. **Role of Ultrasonography in Severe Distal Median Nerve Neuropathy.** *J Clin Neurophysiol.* 2019 Jul;36(4):312-315.

Submitted by Rocio (Carolina) Garcia Santibanez, MD

Edited by Lisa Williams, MD

Electrodiagnostic (EDX) localization of a median mononeuropathy in the distal forearm may be challenging in severe cases with absent evoked median sensory responses and absent motor responses to the APB and lumbricals; abnormal needle electromyography limited to the APB may be suggestive of a localized injury at the carpal tunnel, however, rarely the lesion may be more proximal. This study looked at the use of ultrasound in 46 patients with clinical and electrophysiologic evidence of severe carpal tunnel syndrome (CTS). Patients with peripheral neuropathy and a history of carpal tunnel surgery were excluded. Ultrasound imaging of the median nerve was performed with an 8-18 MHz probe. The cross-sectional area (CSA) of the median nerve was measured using a long axis view along the carpal tunnel measuring from the inlet to the outlet (maximum and minimum diameter D_{max}/D_{min}). The short-axis views were measured at the wrist (CSA_w) and the forearm (CSA_f) using the distal wrist crease and 10cm proximal to the distal wrist crease as land marks. The ultrasonic criteria used for diagnosing median nerve entrapment were $CSA_w > 13mm^2$, $CSA_w/CSA_f > 1.4$, and $D_{max}/D_{min} > 1.3$. In 42 out of the 46 patients, the ultrasound localized the pathology at the wrist. In the other 4 the abnormality was proximal to the wrist (subluxated lunate, neuroma, schwannoma and hamartoma).

Comments: In severe cases of CTS, with nonlocalizable EDX studies (absent evoked sensory responses and absent motor responses), the addition of ultrasonic imaging may be a useful adjunctive tool in confirming entrapment of the median nerve at the carpal tunnel and also detecting pathology proximally that may mimic CTS in the forearm. Although CTS is more common than most alternative diagnoses, the treatment is significantly different for other potential diagnoses and ultrasound may be useful in sorting this out.

September 18, 2019

Power HA, Sharma K, El-Haj M, et al. **Compound Muscle Action Potential Amplitude Predicts the Severity of Cubital Tunnel Syndrome.** *J Bone Joint Surg Am*, 2019; 101:730-38.

Submitted by Elliot Bodofsky, MD

Edited by Nandita Keole, MD

Cubital Tunnel Syndrome is the second most common peripheral nerve compression. There can be demyelination at the ulnar groove, axonal loss, or both. The most commonly diagnostic parameter is Ulnar motor conduction velocity across the elbow. However, loss of Ulnar motor amplitude might correlate better with functional deficits (loss of grip or pinch strength). This was a retrospective study of 83 patients that underwent Cubital Tunnel surgery by a single surgeon between 2013 and 2017. All included patients had a recent NCS at the same teaching institution, and had no other EMG/NCS diagnoses other than Cubital and Carpal Tunnel Syndrome.

Only the First Dorsal Interosseous motor amplitude correlated with preoperative pinch and grip strength. Neither slowing of the Ulnar motor NCV across the elbow, Abductor Digiti Minimi amplitude, nor needle EMG findings correlated with strength. The First Dorsal Interosseous motor amplitude should receive more attention in determining Cubital Tunnel Syndrome severity.

Comments: This article looks at the electrodiagnosis of Cubital Tunnel Syndrome from a surgeon's perspective, arguing that surgery should be performed for objective evidence of weakness. First dorsal interosseous amplitude correlates with grip and to a greater degree, pinch strength, while Ulnar motor NCV across the elbow does not. It is, however, a retrospective study and does not look at patient symptoms.

October 4, 2019

Zhang Y, Fang F. Ann. **Smoking and Amyotrophic Lateral Sclerosis: A Mendelian Randomization Study.** *Neurol* 2019;85:482-484

Submitted by Clark Pinyan, MD

Edited by Nandita Keole, MD

Authors examined the potential causal effect of smoking on ALS using Mendelian randomization method. Genome-wide association study data was reviewed for loci associated with smoking (current or ever smoked). Over 500,000 total participants study data was compared with genomic data from over 12,000 patients with ALS. Based on this method, smokers were found to have a higher risk of ALS compared with non-smokers and provides (further) evidence for a causal relationship.

Genome linkage studies use genetic markers associated with a risk (such as tendency to smoke, cancer, or hypercholesterolemia), compared with incidence of a particular condition, in this case ALS. This can overcome some limitations of traditional epidemiology such as recall or selection bias, by being independent of patient self-reporting or selection. Furthermore, Mendelian randomization can suggest a causative link if certain conditions are met.

In this study, ever smokers were found to have a higher risk of ALS compared to never smokers, which provides further support for more traditional epidemiological studies.

Comments: Epidemiological studies of ALS can be limited by the sometimes rapid progression of the disease, and this provides information on use of new methods of risk analysis. I think it will become increasingly important to understand how to use whole genomic data to determine risk, not only for researchers but soon for clinicians.

October 22, 2019

Svaren J et al. Ann. **Schwann Cell Transcript Biomarkers For Hereditary Neuropathy Skin Biopsies.**
Neurol 2019;85:887-898

Submitted by Clark Pinyan, MD

Edited by Nandita Keole, MD

Authors used quantitative PCR measurements to determine levels of PMP22 mRNA in skin biopsies of patients with CMT1A compared with controls. Though PMP22 mRNA expression is known to be increased in CMT1A affected Schwann cells, its level in biopsies is variable from patient to patient and doesn't correlate well with clinical disease, largely due to variability in number of Schwann cells present. Authors attempted to normalize PMP22 mRNA expression vs. Schwann cell specific genes which are not altered by CMT1A status. This showed reproducible elevations in PMP22 compared to controls.

Comments: Skin biopsy is a commonly used practice for autonomic or small fiber neuropathy, and special staining techniques or analysis may become relevant for specific disorders. As treatments emerge for CMT, skin biopsy may prove a useful marker for treatment response or disease progression.

November 26, 2019

Hans Jürgen Solinski¹, Patricia Dranchak², Erin Oliphant², Xinglong Gu¹, Thomas W. Earnest¹, John Braisted², James Inglese² and Mark A. Hoon. **Inhibition of Natriuretic Peptide Receptor 1 Reduces Itch in Mice.** *Science Translational Medicine* 10 Jul 2019: Vol. 11, Issue 500, eaav5464, DOI: 10.1126/scitranslmed.aav5464.

Submitted by Hristelina Ilieva, MD, PhD

Edited by Elliot Bodofsky, MD

This study uses in vitro and in vivo experimental models to clarify the physiology of itch. Using high-throughput screening human natriuretic peptide receptor one (hNPR1) antagonists were identified, one of which can relieve itch in vivo in mouse models.

Itch stimuli are thought to be detected in the skin by dedicated sensory neurons that express G-protein coupled, Toll-like, and interleukin receptors. Known receptors are many, but the number of cell types that detect it are small and involves two populations – mas-related G protein- coupled receptor A3 (Mrgpra3) and those expressing the neuropeptide natriuretic polypeptide b (NPPB). Both of these classes of neurons transmit itch through a common spinal cord circuit dependent on NPPB. Additionally, sensory neuron-derived NPPB is thought to drive inflammation in different forms of dermatitis, enhancing pruritus. This, together with elevated NPPD levels in renal failure, leads to the choice of NPPB as a target for investigation. NPPB is expressed in a subset of human DRG neurons and is co-expressed with the two receptors hNPR1 and MRGPRX1. High throughput screening identified 15 new hNPR1 antagonists, and these are likely to act as noncompetitive inhibitors of NPR1. One of the compounds readily crossed the blood brain barrier and reached concentrations that predict mouse NPR1 inhibition. Unwanted side effects of NPR1 inhibition were described. NPR1 is expressed in kidney and vasculature. Cardiovascular effects were not present. The authors indicate that future systematic side effects studies are needed.

Comments: Having more specific therapeutic targets than anti-histamine medications, which cause sedation, is a welcome future development. The paper allows a better understanding of the neurophysiology of itch. NM specialists see a variety of neuropathies, particularly uremic neuropathy patients, with very frequent complaints of itching. Being aware of the neurophysiology and that future therapeutic targets exist will be helpful.

December 12, 2019

Vittoria Lombardi, PhD, Giorgia Querin, MD, Oliver J. Ziff, MD, MRCP et al. **Muscle and Not Neuronal Biomarkers Correlate With Severity in Spinal and Bulbar Muscular Atrophy.** *Neurology* 2019; 92:e1205-e1211.doi:10.1212/WNL.0000000000007097
<https://n.neurology.org/content/92/11/e1205>

Submitted by Bryan X. DeSouza, MD

Edited by Elliot Bodofsky, MD

This study prospectively collected blood from 2 cohorts of patients, 93 genetically confirmed SBMA patients, and ALS patients and healthy relatives without neurological symptoms. SBMA and ALS disease severity and progression were evaluated using functional rating scale scores. Progression rate in patients with ALS was calculated as progression rate to last visit (PRL).

AR 100 mice which express the human androgen receptor with an expanded CAG repeat were used. Biomarkers were obtained from male AR100 mice and controls. Patient NfL, CK, and creatinine concentrations were compared, as were mouse NfL levels. Correlations of CK and creatinine levels with SBMAFRS and AMAT scores were assessed.

NfL levels were unchanged and stable over 2 years in 2 independent SBMA cohorts of patients. NfL levels did not show a significant increase in well-established mouse model of the disease over 1.5 years. CK levels (muscle injury marker) were similar in both cohorts and significantly increased compared to ALS patients and healthy controls. CK levels did not differ between slow and fast ALS patients. Creatinine levels (muscle mass marker) were very similar in both cohorts and significantly decreased compared to controls and ALS patients. Creatinine levels significantly correlate with SBMA severity. There was no significant correlation between clinical measures and CK, but creatinine levels strongly inversely correlated with clinical measures both SBMAFRS and AMAT in both SBMA cohorts.

Comments: This is an elegant study with important information, but there are limitations in study design. The authors report that not all data was collected and included in the statistical analysis. The cohort was limited in size, which may affect generalizability of the study results. Thus, a larger prospective study would be needed.

This is an important article for neuromuscular and electrodiagnostic practitioners because biomarkers are commonplace and widely accepted in research as well as clinical practice. In electrodiagnosis, SBMA is characterized by muscle denervation and loss of lower motor neurons in the spinal cord and the brainstem mimicking motor neuron disease. Recent animal research shows a primary myopathic mechanism in this disorder. This study validates the use of serum biomarkers (NfL, CK, and creatinine) in distinguishing neuronal degeneration and muscular disease mechanisms. It also provides strong clinical evidence to support a primary myopathic mechanism in SBMA.