News Science Anthology

January 2020 - December 2020

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

AANEM
American Association of Neuromuscular
& Electrodiagnostic Medicine

News Science
Editorial Board

Anthology of NSEB Journal Article Summaries and Comments
January 2020 - December 2020

About the News Science Editorial Board

This committee helps to highlight significant, timely science news items for AANEM members. Committee members review articles in journals and websites, identify newsworthy items in the field, and write article summaries.

January 9, 2020

Kang, Seok MD; Yoon, Joon Shik MD, PhD; Hong, Suk-Joo MD, PhD; Yang, Seung Nam MD, PhD**. Degree of agreement between electrodiagnostic testing and magnetic resonance imaging in the evaluation of brachial plexopathy**. *American Journal of Physical Medicine & Rehabilitation*. 2019; 98(7):545–548.

Submitted by Rebecca O'Bryan, MD

Edited by Clark Pinyan, MD

Summary: This article reports the findings of a retrospective analysis of 69 patients with symptoms of brachial plexopathy of various etiologies to investigate the degree of agreement between magnetic resonance imaging (MRI) and electrodiagnostic testing (EDX). Of the 69 patients reviewed, 12 were excluded due to diagnoses of other diseases during the assessment, or due to lack of evidence to support the diagnosis on either test (EDX or MRI).

EDX was in all cases performed by a board certified physiatrist or neurologist specialized in peripheral nervous system disorders (the board certification and years of experience were not reported). MRI was reviewed by a musculoskeletal radiologist who was blinded to the patient clinical information.

Results were classified into location along the plexus (preganglionic root, post ganglionic root, trunk, division, cord, and distal branches). An experienced physiatrist made the determination regarding similarities between EDX and MRI based on comparison of anatomic location(s) identified on each test. Patients were then divided into three groups (complete match, partial match, or mismatch).

Results indicated an overall complete or partial match in 63.2% of cases. A mismatch, where either only one modality identified the diagnosis, or where the modalities did not overlap at all in terms of location of lesion, was noted in 36.8% of cases.

In the cases of a mismatch, 16 were due to brachial plexitis, and in 8 of these cases, only one modality revealed an abnormality (6 of the 8 were only apparent on EDX, 2 of the 8 were only apparent on MRI). All 4 of the trauma cases identified as mismatch were only apparent on EDX.

Conclusions drawn from this study were that, overall, MRI and EDX presented in agreement with each other in the evaluation of brachial plexopathy. However, only one test demonstrated the lesion in 12 cases. Time intervals between tests was offered as a potential factor that could cause discrepancy. Each test has its own advantages and disadvantages, and can provide unique information. Discrepencies existed in a fairly significant number of cases, either partially or completely. The testing methods were determined to be complementary in the work up of suspected brachial plexopathy.

Comments: EDX should continue to be a valuable and necessary component to the work up of patients with brachial plexus pathology, even in the event that an MRI has already been performed and localization has been identified. This is especially in cases where the MRI is negative and clinical suspicion is high, as well as milder cases and trauma.

Neuromuscular specialists caring for patients with brachial plexopathy of various etiologies should take from this article further support for their efforts in EDX in the context of work up and surgical or interventional planning. 4 trauma and 6 brachial plexitis cases showed no abnormalities on MRI and localization was only available via EDX (in contrast with only 2 in the brachial plexitis group with abnormalties only on MRI). Advocating for EDX in these patients early and in tandem with MRI may provide enhanced sensitivity and should continue to be employed in patients with symptoms concerning for brachial plexopathy.

January 23, 2020

Joseph P. Donnelly MD; Mazen Hanna MD; Brett W. Sperry MD; William H. Seitz Jr MD**. Carpal tunnel syndrome: A potential early, red-flag sign of amyloidosis.** *J Hand Surg Am.* 2019; 44(10):868-876.

Submitted by Rebecca O'Bryan

Edited by Clark Pinyan, MD

Summary: This article reports on the clinical significance of certain presentations of carpal tunnel syndrome as they relate to the potential earlier diagnosis of amyloidosis in patients with systemic disease. Due to the importance of diagnosing systemic amyloidosis (either light chain or transthyretin), a high index of suspicion is vital in identification and early treatment of these patients.

Presentation of bilateral carpal tunnel syndrome and multiple releases are identified as "red flag" symptoms in men over 50 and women over 60. Biopsy in conjunction with carpal tunnel surgery can reveal amyloid precursor proteins and amyloid deposition both in the connective tissue and within the median nerve itself. With ATTR patients, endoneurial amyloid deposits in the median nerve may directly lead to median neuropathy (as opposed to entrapment as the etiology). Carpal tunnel surgery frequently precedes diagnosis of amyloidosis by many years.

Other concomitant diagnoses may bolster clinical suspicion for systemic amyloidosis (spinal stenosis, biceps tendon rupture, afib/flutter, pacemaker, CHF, family history of ATTR). An algorithm is presented to help provide guidance of value of biopsy in the context of carpal tunnel release.

Comments: Much of the article provides background to the less exposed hand surgeon regarding pathophysiology of the amyloidosis patient, but there is a good review of literature providing background as to the value of a high index of suspicion in a certain population with regards to bilateral and repeat patients with carpal tunnel syndrome. The algorithm is again presented in the context of guidance for the surgical specialist, but this history would be available to the EDX or neuromuscular physician as well, and could be used as a screening tool in the context of providing recommendations within the surgical referral, as well as educational guidance in the context of the neuromuscular specialist to the surgical teams with which we interface and overlap.

This article is an excellent reminder to the EDX physician that a patient presenting with bilateral CTS, especially in the context of previous history of release, a more detailed screening history may be valuable in recommending to the surgical team that a biopsy be sent to potentially identify amyloidosis patients early in the process. This may allow for an earlier intervention in the disease progression, possibly significantly improving prognosis and quality of life in this patient population.

February 10, 2020

Christopher J. Dy MD, MPH; Kate Peacock BS; Margaret A. Olsen PhD, MPH; Wilson Z. Ray MD; David M. Brogan MD, MS. **Frequency and risk factors for prolonged opioid prescriptions after surgery for brachial plexus injury.** *The Journal of Hand Surgery*. 2019; 44(8):662-668.

Submitted by Rebecca O'Bryan, MD

Edited by Clark Pinyan, MD

Summary: This article reports the results of an extensive retrospective analysis of data for 1,936 patients that underwent surgery for a brachial plexus injury (BPI) investigating potential identifiable risk factors for prolonged opioid use postoperatively.

The authors reviewed a de-identified database to extract patients with coded brachial plexus injury and subsequent brachial plexus or peripheral nerve surgical intervention. Risk factors included: diagnoses of depression, anxiety, drug abuse, tobacco use, and preoperative use of opioids and neuropathic pain medications. Control group was formed utilizing patients matched by age, sex and year to provide baseline data regarding opioid and neuropathic pain medication prescribing habits. Multivariate linear regression modeling was employed to examine relationships between the above mentioned factors and prolonged opioid (primary dependent) and neuropathic (secondary dependent) pain medication prescribing. Subgroup analysis evaluated the effect of opioid naïveté).

27% of BPI patients had prolonged opioid prescribing (defined as 90-180 days post index date), with 10.8% of patients opioid naïve prior. Predictors of prolonged postoperative opioid prescriptions in BPI patients were preoperative opioids, preoperative neuropathic pain medication use, histories of drug abuse, tobacco use, and anxiety. Most important factor was determined to be preoperative use of opioids.

Comments: This article provides detailed statistical information regarding risk factors for potential prolonged opioid prescribing in the brachial plexus injury patient post operatively. Significant questions remain due to the methods employed in identifying and defining the "prolonged opioid prescription" group, as these patients were identified utilizing data from *prescriptions filled*, not actual data on patient utilization. These prescriptions may not have been utilized, may have been diverted, or may not have been effective. Due to the retrospective nature of this study, no information is available regarding prescriber decision-making and patient outcomes with respect to prescribing of controlled medications. Interestingly, only 12.2% of the BPI patients had prolonged neuropathic pain medication prescriptions. This is attributed to potential poor long-term tolerance of these medications; however, in my experience, this may in fact be due to lack of education or facility in the prescription of these medications by the surgical providers.

Opioids are third line medications in the management of neuropathic pain, and many options can and should be employed in the management of BPI pain prior to their introduction. Identification of risk factors for long term use and potential abuse may help the neuromuscular physician on the team in recommendation of medications for pain management, with the goal of minimizing long term prescription opioids whenever possible. Education of surgical specialists in the use of neuropathic pain medications with lower risk of abuse and dependency would also be beneficial.

February 24, 2020

Issar T, Arnold R, Kwai NC, et al. **Relative contributions of diabetes and chronic kidney disease to neuropathy development in diabetic nephropathy patients**. *Clinical Neurophysiology*. 2019; 130:2088-2095.

Submitted by Elliot Bodofsky, MD

Edited by Clark Pinyan, MD

Summary: Distal Symmetric Polyneuropathy (DSP) is a common complication of both Type 2 diabetes (T2DM) and chronic kidney disease (CKD). Diabetic kidney disease (DKD) is the most common cause of CKD. The combination of T2DM and kidney disease (DKD) is believed to cause more rapid progression of neuropathy than either alone, but the relative contributions of DM and renal disease are not clear.

This study recruited 41 normal subjects, 40 with T2DM and normal renal function, 28 with CKD and no DM, and 30 with DKD. The groups were age and gender matched. The two DM groups showed no difference in DM duration, BMI or glycemic control. Renal function matched between the CKD and DKD groups. Patients were evaluated using the 8-point Total Neuropathy Scale (TNS). This includes neuropathy symptoms, physical examination, Sural and Tibial NCS. Median Nerve excitability testing was performed to indirectly assess ion channels, energy-dependent pumps, and axon membrane exchangers.

Patients with DKD had much higher TNS neuropathy scores than patients with T2DM or CKD. T2DM and CKD patients had similar scores. Sural and Tibial NCS showed the greatest abnormalities of any TNS criteria. There were no significant differences between DKD and T2DM and CKD groups in symptoms, but some significant differences in physical exam. Nerve excitability studies also showed that DKD patients had the greatest abnormalities. The DKD excitability pattern was more similar to CKD than TSDM.

Comments: T2DM and CKD are very common causes of DSP. The combination, DKD, is unfortunately also quite common in clinical neurophysiology practice. DKD patients often want to know which condition(s) caused their neuropathy. This study shows that both conditions are contributing, although the DKD pattern is a bit more like renal neuropathy. Crucially, the data indicate that NCS assesses the severity of DSP far better than symptoms or physical examination.

Libonati L, Barrone TF, Ceccanti M, et al. **Heteronymous H reflex in temporal muscle as a sign of hyperexcitability in ALS patients.** *Clinical Neurophysiology.* 2019; 130:1455-1459.

Submitted by Elliot Bodofsky, MD

Edited by Clark Pinyan, MD

Summary: Amyotrophic Lateral Sclerosis (ALS) is a severe neurodegenerative disorder involving both upper and lower motor neurons (UMN and LMN). Diagnosis is mainly clinical, and takes an average of one year after the onset of clinical symptoms. Diagnostic tests are limited. EMG/NCS shows only LMN involvement in affected regions. Better diagnostic tools are needed. Stimulation of the Masseteric nerve can induce an H Reflex in the Masseter and the temporal muscles. In normal subjects, the Temporal H Reflex is usually only seen with muscle contraction. But it can be seen at rest in ALS with corticonuclear tract involvement.

This study involved 36 patients with definite or probable ALS by standard criteria, and 52 subjects without evidence of neurologic disease or on medications that might affect the test. There were no significant demographic differences between the groups. Needle stimulation of the Masseteric nerve between and condyle and coronoid process of the mandible was used, with surface pickup over the belly of the Temporalis and reference over the forehead.

The Temporalis H Reflex was found in 32/36 (88.9%) of ALS patients and none of the normal subjects. There were no differences in presence between patients with predominantly UMN versus LMN symptoms. This test is quick and fairly inexpensive. Overall, the presence of a resting Temporalis H Reflex may assist in the diagnosis of ALS in patients with predominantly LMN symptoms.

Comments: ALS is a relatively common, severe, and rapidly progressive disorder. It can be difficult to diagnose in the early phases. The Temporalis H Reflex appears to be a quick, sensitive, and specific test that may help detect it sooner. However, this study included a variety of ALS patients, so it is not clear whether the very high sensitivity would be seen in early cases.

March 23, 2020

Evdokimov D, et al**. Reduction of skin innervation is associated with a severe fibromyalgia phenotype.** *Ann Neurol.*

Submitted and Edited by Clark Pinyan, MD

Summary: Patients with clinical diagnosis of fibromyalgia underwent extensive testing of small and sensory nerve fibers, including proximal and distal lower extremity skin biopsy, corneal nerve microscopy, quantitative sensory testing, pain-related evoked potentials and microneurography. Patients with other neuropathic or potentially neuropathic diseases were excluded. Controls included patients with a clinical diagnosis of major depressive disorder with pain (MD-P) as well as lab normative values for skin biopsy. 63% of fibromyalgia syndrome patients had reduced intraepidermal nerve fiber density compared to 10% of MD-P patients and 18% of controls. Those with reduced fiber density had higher pain intensity, higher impairment due to pain, higher disease burden, more stabbing pain and paresthesias, and more anxiety. Therefore the extent of small fiber pathology may correlate with symptom severity in fibromyalgia.

Comments: The diagnosis of "fibromyalgia" is very complex, especially how it is often applied in clinical practice. It is sometimes difficult to distinguish or separate from other possible causes of body pain, fatigue, and hyperalgesia. This article helps elucidate the detectable, physiologic differences between fibromyalgia syndrome and other painful disorders such as MD-P, as well as attempt to find a basis for symptom severity in some patients. It certainly may not apply to all patients with this clinically diverse syndrome, but could give us some hints as to causation as well as help direct therapy or develop new therapies. Anything that hints at a physiologic basis or reproducible changes in fibromyalgia would be helpful for clinicians who encounter this common syndrome.

April 6, 2020

Pane M, et al. **Nusinersen in type 1 spinal muscular atrophy: Twelve-month real-world data.** *Ann Neurol.* 2019; 86:443-

451.

Submitted and Edited by Clark Pinyan, MD

Summary: Nusinersen is an antisense oligonucleotide therapy for spinal muscular atrophy (SMA), which targets the SMN2 pre-messenger RNA to increase production of SMN2. Although initially indicated for use in all ages, initial trials showed improvement was greater in younger patients with milder disease. This Italian study followed 85 patients 12 months from nusinersen therapy, with severity ranging from severe to mild, and age at treatment from 2 months to 15 years, 11 months. Although less than 15% of patients experienced some functional decline, over 60% improved at least 2 points on the CHOP INTEND scale, with continued improvements in the second six months. Gains were greatest for children under 24 months, but smaller gains still seen for older patients. No significant gains were noted in the most severe phenotypes. Caregiver questionnaires obtained from 72 families reported subjective overall stability (11) or increased function (61).

Comments: For a revolutionary therapy in a rare disease, it takes time to fairly assess the impact, as well as clearly define the population that would benefit. This article demonstrates some benefit for populations at an expanded age range, though magnitude and duration still remain to be seen. Several of our members are already administering nusinersen in specialty clinics. We need clearer data to help set patient and family expectations and plan for future therapy.

April 17, 2020

Turner MR, Barohn RJ, Corcia P, et al. **Primary lateral sclerosis: consensus diagnostic criteria.** *Journal of Neurology, Neurosurgery & Psychiatry.* Published Online First: 06 February 2020. doi:10.1136/jnnp-2019-322541.

Submitted and Edited by Francisco Gomez, MD

Summary: Primary Lateral Sclerosis (PLS) is a neurodegenerative disease affecting upper motor neurons primarily. This disease tends to affect around age 50, initiating with gait difficulties progressing to spastic paraparesis. Other initial symptoms may include corticobulbar dysfunction, cognitive dysfunction or pseudobulbar affect as well as urinary symptoms. Cognitive function loss, and especially signs of frontotemporal dementia may be less frequently observed, as compared to ALS.

Diagnosis may prove challenging as PLS can closely mimic amyotrophic lateral sclerosis or hereditary spastic paraparesis and there is no clear histopathological distinction between PLS and the ALS in and there is controversy about whether these two diseases are part of a common pathological continuum. A delay to diagnosis is commonly observed, as previous criteria required a disease progression of 3-5 years.

Age >25 years and the presence of: progressive upper motor neuron (UMN) dysfunction for a minimum of 2 years in at least 2 out of 3 regions: lower extremity, upper extremity, bulbar. The absence of sensory symptoms, signs of active lower motor neuron degeneration†, no alternative diagnosis. Under the proposed criteria, Probable PLS is defined by the absence of significant active LMN degeneration at 2–4 years from symptomatic debut, and Definite PLS is defined by the absence of significant active LMN degeneration 4 or more years from onset.

Comments: The authors also offer a tour de force on emergent diagnostic technologies in the diagnosis if PLS. Transcranial Magnetic Stimulation demonstrate longer conduction times and decreased cortical excitability in PLS, differentiating this entitity from PLS and Hereditary Spastic Parapareis, respectively. As neurofilaments have emerged as a biomarker of neuronal degeneration, PLS has exhibited less levels of these markers, as compared to ALS. The authors further described emerging MRI volume quantifying technology as a method to better detect PLS mediated prefrontal gyrus degeneration.

While PLS is a relatively rare disease, simplified diagnostic criteria permitting earlier diagnosis of a disease which is so similar clinically to other entities is a boon to both clinicians and patients anxious for a diagnosis. They may also decrease practice variation and may aid in the recognition of this disease however, they remained to be verified in real world application.

May 4, 2020

Montembeault M, Sayah S, Rinaldi D, et al. **Cognitive inhibition impairments in presymptomatic C9orf72 carriers.** *Journal*

of Neurology, Neurosurgery & Psychiatry. Published Online First: 13 February 2020. doi:10.1136/jnnp-2019-322242.

Submitted and Edited by Francisco Gomez, MD

Summary: Nucleotide repeat expansions in the *C9orf72* gene are a frequent cause of frontotemporal dementia and amyotrophic lateral sclerosis. Some authors have described cognitive dysfunction in C9orf72 patients preceding debut of motor symptoms related to ALS.

The authors sought to further elucidate relationships between cognitive impairment, motor symptomatology, and MRI findings. They included 38 C9orf72 patients younger than 40 years as well as 22 ALS controls.

Cognitive evaluation pertaining to cognitive inhibition was performed. Cognitive inhibition refers to the ability to resist interference from irrelevant stimuli while performing tasks, considered crucial to everyday living. The Hayling Sentence Completion Test (HSCT) is considered quite sensitive for said function and a predictor of everyday functioning and has been associated with frontal lesions on imaging. Thus, the authors propose early cognitive changes may be not only detectable via the HSCT but may also correlate with early MRI findings, which showed cerebellar volume loss in post-hoc volumetric analysis.

The authors found C9orf72 patients <40 years of age exhibited slower completion and increased errors in the HCST not seen in the control group. Furthermore, HCST completion times significantly predicted symptomatic debut. Notably, HCST completion time also correlated with cerebellar volume loss in post-hoc analysis further highlighting the involvement of the cerebellum in cognition.

Comments: Overall, the authors succeeded in integrating clinical testing with imaging findings in a novel way with direct clinical applications. HCST may offer a new tool for screening, evaluation and monitoring of C9orf72 patients. Early detection of symptoms may offer new avenues to patients, and may lead to earlier interventions, and we can now avail ourselves of a validated and easily performed test which can significantly predict symptomatic onset in their patients.

May 18, 2020

Ingrid J.T. Herraets, MD,* H. Stephan Goedee, MD, PhD,* Johan A. Telleman, MD,* Ruben P.A. van Eijk, MD, J. Thies van Asseldonk, MD, PhD, Leo H. Visser, MD, PhD, Leonard H. van den Berg, MD, PhD, and W. Ludo van der Pol, MD, PhD. **Nerve ultrasound improves detection of treatment-responsive chronic inflammatory neuropathies.** *Neurology* 2020; 94:1-10.

Submitted by Bryan DeSouza, MD

Edited by Francisco Gomez, MD

Summary: The authors had previously shown brachial plexus and median nerve enlargement were reliably discoverable via ultrasound in patients with inflammatory neuron. Authors evaluated diagnostic accuracy of nerve ultrasound in a prospective study including 100 consecutive patients, with aim of determining whether ultrasound in as well as nerve conduction studies can aid in detecting treatment-responsive patients. Patient included were under suspicion of chronic inflammatory neuropathies (CIN), including CIDP and variants (Lewis Sumner syndrome, and Multifocal Motor Neuropathy).

100 consecutive patients referred for suspected CIN were evaluated by nerve ultrasound (NUS), standardized nerve conduction studies (NCS) and other diagnostic tests. A diagnosis of CIN variants was established upon fulfillment of clinical criteria, NCS, NUS and or treatment response criteria was met. NUS criteria was determined as enlargement, that is increased in cross section of a nerve was found at 1 or more of the measured sites set at proximal median nerve and brachial plexus.

The cohort was divided into 4 groups based on NCS and NUS findings, and monitored over one year save group 3 whom were excluded.

	NCS	Ultrasound	Number of patients
Group 1	+	+	31
Group 2	+	-	3
Group 3	-	-	41
Group 4	-	+	25

A diagnosis of chronic inflammatory neuropathy was established in 38 patients. Sensitivity and specificity of nerve ultrasound and NCS were 97.4% and 69.4% and 78.9% and 93.5%, respectively. Investigators found that 8/38 patients with normal NCS yet abnormal NUS responded to treatment. They concluded that NUS was highly sensitive, discovering an additional 21.1% of CIN that subsequently responded to treatment.

Comments: The importance of this study cannot be understated, given NUS is an emerging technique with an increased sensitivity over NCS. NUS also offers greater patient comfort, as a non-invasive evaluation method, and may incur decreased costs and shorter exam time. If these results can be replicated in Class I or II studies, then ultrasound may be incorporated in the EFNS/PNS diagnostic criteria for CIDP. Clinicians should then strongly consider adding this technique to their practice. The ability to detect additional cases of CIN that would otherwise be missed and more importantly, offer treatment and an improved quality of life to several patients whom may otherwise go undiagnosed.

May 29, 2020

Adrichem ME1, Bus SR1, Wieske L1, Mohammed H2, Verhamme C1, Hadden R2, van Schaik IN1, Eftimov F1. **Combined intravenous immunoglobulin and methylprednisolone as induction treatment in chronic inflammatory demyelinating polyneuropathy (OPTIC protocol): A prospective pilot study**. *Eur J Neurol.* 2020; 27(3):506-513.

Submitted by Nandita Keole, MD

Edited by Francisco Gomez, MD

Summary: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune mediated neuropathy causing appendicular sensorimotor. Treatment of CIDP frequently consists of immunomodulation via IVIg or steroids, however an efficacious and cost-effective treatment regime has proven elusive. In this non-controlled open-label pilot study, which is to precede a randomized control trial, authors sought to test a combined IVIg and IV methylprednisolone (IVMP) regimen.

They included 20 **c**onsecutive treatment-naive patients with chronic inflammatory demyelinating polyradiculoneuropathy (diagnosed as per European Federation of Neurological Societies/Peripheral Nerve Society criteria), of which 17 completed the treatment schedule. Remission was defined as improvement at 18 weeks without the need for further immune treatment between end of the treatment schedule and 1 year follow-up and set as the primary outcome.

Participants were then treated with IVIg, 2 g/kg loading dose and 1 g/kg maintenance treatment every 3 weeks, combined with 3 weekly 1g IV methyl prednisolone infusions, for a total of 18 weeks. The cumulative steroid dose was 7g. All patients underwent osteoporosis prophylaxis with alendronate and vitamin D.

Improvement was defined as a minimal clinically important difference on the Inflammatory Rasch-Built Overall Disability Scale and/or an increase of ≥8 kPa in grip strength between baseline and week 18. A total of 13 (76%) of patients showed improvement at 18 weeks of treatment initiation and 10 (59%) exhibited remission at 1 year. Short-term combined induction treatment with IVIg and IVMP induced remission in almost 60% of patients who completed the treatment schedule. Combined induction therapy was generally well tolerated, although 4 patients suffered serious adverse events.

Comments: The investigators found combination treatment of IVIG and IVMP may be effective in the treatment of CDIP and lead to sustained remission at 1 year. A treatment schedule lasting only 18 weeks and providing clinical improvement would be a boon to our patients whom would otherwise suffer a protracted course of CIDP and also reduce total IVIG administered and concurrent costs.

A randomized control trial is currently underway to further test this treatment schedule, which shows promise.

Mori L1,2, Signori A3, Prada V1, Pareyson D4, Piscosquito G5, Padua L6, Pazzaglia C7, Fabrizi GM8, Picelli A9, Schenone A1,2; TreSPE study group. **Treadmill training in patients affected by Charcot-Marie-Tooth neuropathy: Results of a multicenter, prospective, randomized, single-blind, controlled study.** *Eur J Neurol.* 2020; 27(2):280-287.

Submitted by Nandita Keole, MD

Edited by Francisco Gomez, MD

Summary: A multicenter, prospective, randomized, single-blind, controlled study of 53 outpatients affected by CMT1A who were recruited and randomized in two treatment groups: one underwent stretching and proprioceptive exercise (SPE), whereas the other was additionally treated with treadmill training (TreSPE). Primary outcome measures (OMs) were the walking evaluations and secondary OM was the balance assessment. All participants were assessed at baseline and after 3 and 6 months of treatment. Most patients showed an improvement in at least one OM after 3 months [42/47 (89.4%)] and 6 months [38/40 (95%)] of treatment. No adverse events were reported in either group.

Rehabilitation treatment produces an objective benefit in people with CMT disease, both proprioceptive and stretching exercise as well as treadmill training. The authors found that there was deterioration in both groups at about 6 months so recommendations could be made for twice a year therapy. Patients with CMT disease who undergo rehabilitation treatment may have benefits such as prevention of secondary impairments, maintaining articular range of movement, avoiding pain and contractures, and maximizing remaining abilities.

Comments: Interesting article because the authors found that just stretching and balance exercises alone significantly improved patient abilities. Patients can be instructed in a home exercise program that would be of benefit to them.

A caveat is that the therapy was provided twice a week for 12 weeks (24 sessions) – not sure if we can get patient buy-in for that many weeks of therapy.

June 26, 2020

Holzgrefe RE, Wagner ER, Singer AD, Daly CA. **Imaging of the peripheral nerve: Concepts and future direction of magnetic resonance neurography and ultrasound.** *J Hand Surg Am.* 2019; 44(12):1066-1079. doi: 10.1016/j.jhsa.2019.06.021. Epub 2019 Oct 2.

Submitted by Rebecca O'Bryan, MD

Edited by Francisco Gomez, MD

Summary: This review article provides an overview of the most current concepts in peripheral nerve imaging in the context of nerve injury and compressive neuropathies. It goes into some detail with regards to the application of each modality (ultrasound and magnetic resonance neurography), and then provides direction about imaging choices based on the clinical picture. It also puts into context the usefulness given the availability of electro-diagnostics. In the context of compressive neuropathies, recommendation is to utilize ultrasound in the setting of recurrent pathology, atypical presentations, when the diagnosis is unclear, and in patients who cannot tolerate electro-diagnostics. MRN is the imaging modality of choice in traumatic nerve lesion, brachial plexus injuries, and nerve tumors. Emerging imaging modalities are also reviewed (sonoelastography, diffusion tensor imaging and tractography, 3D volume neurography and cinematic rendering, microneurography, and contrast agents).

Comments: AANEM members are already utilizing ultrasound and MRN technology to supplement electrodiagnostic evaluation. This article provides a fairly comprehensive review of these modalities and also reviews state of the art, emerging imaging strategies for our patients with peripheral nerve pathology.

Tan C, Yukari S, Khena-Jin G, et al. **A model to predict the probability of acute inflammatory demyelinating polyneuropathy.** *Clinical Neurophysiology. 2020;* 131:63-69.

Submitted by Elliot Bodofsky, MD

Edited by Francisco Gomez, MD

Summary: The goal of this research was developing a predictive model to differentiate acute inflammatory demyelinating polyneuropathy (AIDP) from non-demyelinating Guillain-Barré syndrome (GBS), based on NCSs performed at 1-20 days after onset and at 3-8 weeks. There were 90 patients, 40 with AIDP and 50 with non-AIDP GBS. Testing included median and ulnar motor and sensory, tibial motor, and sural sensory. There were significant differences between the two groups on almost all parameters, except for the sural nerve. A predictive model was constructed using just 3 parameters; median motor nerve conduction velocity, ulnar distal motor latency, and sural sparing (abnormal ulnar/normal sural). A 0-6 total point scoring system for these criteria yielded an AUC of 0.862 and 0.885 for the early and late NCS. The later NCS test had a positive predictor value for AIDP of 93% for a score of 2 or greater and 98% for 3 or greater.

Comments: This article outlines a simple and relatively straightforward way of determining long term prognosis in GBS, a common disorder. The amount of needed testing is rather modest. Accuracy is high. This appears to be a rather efficient way of evaluating these cases.

August 17, 2020

Gentile L, Coraci D, Pazzaglia C, et al. **Ultrasound guidance increases diagnostic yield of needle EMG in plegic muscle.** *Clinical Neurophysiology*. 2020; 131:446-450.

Submitted by Elliot Bodofsky, MD

Edited by Francisco Gomez, MD

Summary: Major peripheral nerve injury is common and quite disabling, and the detection of early reinnervation is crucial in determining prognosis and treatment. Standard needle EMG involves random muscle needle insertion, and hence can miss minimal residual muscle activity. There were 41 recent nerve trauma patients with no muscle activity on clinical exam and EMG/NCS (three needle insertions at 10 points each), that returned for follow up. Ultrasound (US) was not performed at the initial evaluation due to swelling, bruising and pain. At a 2-3 month follow up, 22 out of 41 patients showed a CMAP and/or active motor units on needle EMG. In 9/19 (47%) with no activity on EMG/NCS, motor activity was found on US. In the 10 patients with no activity on EMG/NCS and US, follow up at 4-6 months detected muscle activity in 2 on both studies. Overall, the specificity of testing was higher using US in addition to EMG/NCS.

Comments: The addition of US testing detected muscle activity in almost half of major nerve trauma patients with no activity on EMG/NCS. This is crucial in determining whether surgery is needed in many cases. US should be performed in all cases of major nerve trauma with no evidence of motor activity on EMG/NCS.

September 1, 2020

Mariosa D, Kamel F, Bellocco R, et al. **Antidiabetics, statins, and the risk of amyotrophic lateral sclerosis (ALS)**. *Eur J Neurol*. 2020; 27(6):1010-1016. doi:10.1111/ene.14190.

Submitted by Nandita Keole, MD

Edited by Francisco Gomez, MD

Summary: Drugs used to treat glucose or lipid metabolism have been suggested as risk factors for ALS. Population based case control study (5 controls for each case of ALS) done in Sweden to examine the association between statins, antidiabetics and subsequent development of ALS. Study examined cases from July 2006 to Dec. 2013 from national database. Prescriptions filled for years prior to diagnoses was examined using a national prescription database. They found that patients with ALS were less likely to have been prescribed antidiabetics and there was no association with statins overall though in women statins were prescribed the year before diagnoses of ALS. This per authors may point to a risk of accelerated course of ALS in patients who have been prescribed statins.

Comments: This study suggested that antidiabetics have a protective effect for ALS- could prove a pathway for treatment or risk mitigation.

September 14, 2020

Vallat JM, Mathis S, Vegezzi E, et al. **Antibody and macrophage-mediated segmental demyelination in chronic inflammatory demyelinating polyneuropathy (CIDP): Clinical, electrophysiological, immunological, and pathological correlates**. *Eur J Neurol.* 2020;27(4):692-701. doi: 10.1111/ene.14133.

Submitted by Nandita Keole, MD

Edited by Francisco Gomez, MD

Summary: Retrospective study of immune reactivity to myelin in 94 patients with diagnoses of CIDP (diagnosed according to the European Federation of Neurological Societies and the Peripheral Nerve Society criteria including electrophysiological criteria). Nerve biopsy was done for those who did not fulfil these criteria at first assessment. Study was conducted in France. Sural nerve biopsies were examined using immunofluorescence and electron microscopy. It was found that many patients presented a strong IgG or IgM reactivity toward the myelin compartment and evidence of complement C3d deposition, confirming the autoimmune etiology. 9 patients needed nerve biopsy to confirm CIDP. These nerve segments were evaluated under electron microscopy and showed myelin sheath phagocytosis by macrophages in intermodal region. Per authors this data demonstrates that antibody and macrophage mediated segmental demyelination is involved in the pathogenesis of some patients with CIDP and is responsible for segmental demyelination, slowing and temporal dispersion.

Comments: Interesting to correlate NCS findings with immunological and histochemical changes. Mainly of academic interest.

September 30, 2020

Provitera V, et al. **A model to study myelinated fiber degeneration and regeneration in human skin.** *Ann Neurol.* 2020;87:456-465.

Submitted by Clark Pinyan, MD

Edited by Francisco Gomez, MD

Summary: The authors sought to describe changes with degeneration and regeneration of large myelinated fibers and Meissner corpuscles (MC) in a cohort of patients with median nerve compression at the wrist, pre and post-surgery. 30 patients with moderate median nerve compression scheduled for surgery underwent clinical assessment, qualitative sensory testing, electrodiagnostic (EDX) testing, and a 2mm biopsy from the third digit fingertip. Biopsies were compared to 30 matched controls. Clinical and EDX assessments were repeated in the study group at 12 month follow up, and 15 patients underwent repeat biopsy. Presurgical patients demonstrated a decreased density of intraepidermal nerve fibers and intrapapillary myelinated endings. Myelinated fibers showed caliber reduction and nodal elongation. MC had normal density but were smaller, located deeper in the dermis and capsule appeared partially empty. In follow up, the caliber of intrapapillary myelinated endings was increased, MC appeared more filled, but remained deeper in the dermis. Vasoactive intestinal peptide-reactive fibers were more superficial. At onset, clinical symptom severity correlated with myelinated fiber nodal gap length, MC size, density, and depth.

Comments: This study describes changes in large, myelinated fibers in a naturally occurring degenerative and regenerative model, using changes that can be seen in glabrous skin (as opposed to small intraepidermal fibers in a hairy skin biopsy).

October 14, 2020

Villar-Quiles RN, et al. **ASC-1 is a cell cycle regulator associated with severe and mild forms of myopathy.** *Ann Neurol.*

2020;87:217-232.

Submitted by Clark Pinyan, MD

Edited by Francisco Gomez, MD

Summary: Dysfunction of the transcriptional coactivator ASC-1 (activating signal cointegrator 1) complex has been demonstrated in forms of ALS, SMA, and congenital myopathies. Mutations in TRIP4 gene, which encodes ASC-1, has been described recently in a family with congenital myopathy. This study assesses 5 different families with 7 novel TRIP4 mutations. All mutations caused ASC-1 depletion. Clinical phenotype was purely myopathic, ranging from lethal neonatal to mild ambulatory adult. Muscle biopsies showed multiminicores, nemaline rods, cytoplasmic bodies, caps, central nuclei, rimmed fibers and / or mild endomysial fibrosis. ASC-1 depletion in CSC12 and patient-derived fibroblasts and muscles caused accelerated proliferation, altered expression of celll cycle proteins, and /or shortening of the G0/G1 cell cycle phase leading to cell size reduction.

Comments: There is increasing recognition that ASC complex and other transcriptional modulators are important in pathological processes whether acquired or inherited. Defining the range of disease associated with defects in this gene may lead to understanding the final common pathologic mechanisms and potential interventions.

October 26, 2020

Amanda C. Guidon, MD, Anthony A. Amato, MD. **COVID-19 and neuromuscular disorders**. *Neurology*® 2020; 94:959-969.

doi:10.1212/WNL.0000000000009566.

Submitted by Bryan DeSouza, MD

Edited by Francisco Gomez, MD

Summary: Drs. Guidon and Amato provide a timely review of the COVID-19 pandemic's potential effects on patients with neuromuscular disorders. They cover the broad spectrum of how the pandemic affected the delivery of neuromuscular care to education and research. This article reviews potential neuromuscular complications of COVID-19, assessment and mitigation of COVID-19-related risk for patients with preexisting neuromuscular disease, guidance for management of immunosuppressive and immunomodulatory therapies, practical guidance in neuromuscular care, telemedicine, education, and its effect on neuromuscular research.

Comments: This article provides a methodical approach to the evaluation and management of our patients with guidance in immunosuppressive and immunomodulatory therapies. It strongly emphasizes the need for a team-based and multidisciplinary collaboration for care.

November 11, 2020

Ling Mao; Huijuan Jin; MengdieWang; Yu Hu; Shengcai Chen; Quanwei He; Jiang Chang; Candong Hong;Yifan Zhou; DavidWang; Xiaoping Miao; Yanan Li, MD, PhD; Bo Hu, MD, PhD. **Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China**. *JAMA Neurol.* 2020: 77(6):683-690.

Submitted by Niranjan Singh, MD

Edited by Francisco Gomez, MD

Summary: This is a retrospective analysis of 214 patients from Wuhan, China with COVID-19, 126 patients (58.9%) non severe infection and 88 patients (41.1%) had severe infection according to respiratory status. Overall the manifestation of symptoms where classified into central nervous system-dizziness, headache, impaired consciousness, stroke, ataxia and seizure, peripheral nervous system-taste impairment, smell impairment, vision impairment and nerve pain, and skeletal muscle injury manifestation. Overall, 36.4% (78 patients) have had some short of neurologic manifestation. Peripheral nervous system involvement 8.9 %, impairment of taste 5.6 %, smell 5.1 %, vision 1.4% nerve pain 2.3 %, skeletal muscle injury 10.7 %, and headache 13.1 %. In patients with more severe infections, neurologic manifestations included acute stroke 5.7 %, impaired consciousness 14.8%, and skeletal muscle injury 19.3 %.

Comments: The finding that many patients presented early with neurologic symptoms, such as anosmia, ageusia, and myopathy, along with less severe respiratory symptoms suggests that neurologists may be confronted by patients presenting with new-onset neurologic symptoms. Reports have emphasized anosmia as a common early feature of COVID-19 illness, as in many upper respiratory tract infections. This small series may not reflect the entire spectrum of neurologic disease in COVID-19 disease.

November 24, 2020

Omejec G, Podnar S. **Utility of nerve conduction studies and ultrasonography in ulnar neuropathies at the elbow of different severity**. *Clinical Neurophysiology.* 2020; 131:1672-1677.

Submitted by Elliot Bodofsky, MD

Edited by Francisco Gomez, MD

Summary: This study compared ultrasound (US), short segment nerve conduction studies (SSNCS), and 10 cm NCS across the elbow, for detection and localization of ulnar nerve compression at the elbow (UNE). Patients that were included had either numbness or paresthesia in the 4th and 5th finger, weakness in ulnar innervated muscles, or reduced hand dexterity. Those with previous elbow trauma, cervical radiculopathy, polyneuropathy, or evidence of ulnar compression at the wrist were excluded. There were 202 arms from 197 patients. Clinical severity was assessed.
All three techniques had high sensitivity for clinically moderate and severe cases. All showed low sensitivity for clinically very mild cases (sensory symptoms only), and moderate sensitivity for mild cases. SSNCS had a significantly higher sensitivity for moderate and severe UNE than US. There were no significant differences between the techniques for accuracy of localizing UNE. US cross section area increased with more severe UNE, but was significantly larger only in severe cases. By contrast, SSNCS and 10 cm across elbow NCS velocity were both lower as clinical severity became more severe. Of note, the study design did not allow specificity to be calculated. Overall, NCS appears to be somewhat more sensitive than US in detecting UNE.

Comments: A very good study comparing US and NCS techniques for detection and localization of UNE, a very common problem in neurodiagnostic practice. Utilizes clinical presentation as the standard. Had very few clinically mild cases. Overall, neither NCS nor US were very sensitive for mild UNE.