

REHAB IN REVIEW

WWW.REHABINREVIEW.COM

TM

Volume 29 Number 2

Published by Physicians
In Physical Medicine and Rehabilitation

February 5, 2020

THE CYCLOPS SYNDROME AFTER ACL REPAIR

Following anterior cruciate ligament (ACL) reconstruction, a nodule of fibrovascular tissue anterior to the graft can be observed. This has been described as a cyclops lesion. These phenomena are often accompanied by a snapping and catching while walking. This study evaluated the risks of, and morbidity associated with, a cyclops lesion.

This retrospective study collected data from a prospective study, the SANTI study of a group of patients undergoing primary ACL repair between 2011 and 2017. Subjects were required to have gained full knee extension and to be able to demonstrate adequate quadriceps activation after surgery. All patients received the same postoperative rehabilitation protocol, with the goal of returning to contact sports at eight to nine months.

Physical examinations were conducted preoperatively and at postoperative intervals for up to one year. The presence of a knee extension deficit was evaluated at each follow-up, with an MRI obtained after three months in patients who had symptomatic extension deficits. If a cyclops lesion was present, it was arthroscopically removed.

Of the 3,633 patients in the study, 65 developed a cyclops syndrome, with all recovering full knee extension after treatment. The univariate analysis found that factors reaching the 25% threshold of correlation with the cyclops syndrome included knee extension deficit at three and/or six weeks, body mass index of greater than 25 kg/m² and the presence of bimeniscal lesions. A multivariate analysis indicated that only knee extension deficits at three and six weeks were associated with a significant increase in risk of the development of a cyclops lesion.

Conclusion: This study of patients undergoing ACL repair found that an extension deficit in the early postoperative period was a significant

predictor of the development of a symptomatic cyclops lesion.

Delaloye, J., et al. Knee Extension Deficit in the Early Postoperative Period Predisposes to Cyclops Syndrome after Anterior Cruciate Ligament Reconstruction. A Risk Factor Analysis in 3,633 Patients from The SANTI Study Group Database. *Am J Sports Med.* 2020. <https://doi.org/10.1177/0363546519897064>.

DEXMEDETOMIDINE AND POSTOPERATIVE COGNITION

Subjects were 65 years of age or older, all scheduled for a total knee arthroplasty (TKA). The group was randomly assigned to receive anesthesia with either propofol or dexmedetomidine. The primary outcome measure was the incidence of post-operative delirium (POD), as assessed during the first week after surgery. Venous blood was assessed for indicators of inflammation including concentrations of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha) and S100 beta, conducted before anesthesia and at 12, 24- and 48-hours post-surgery.

The incidence of POD was less in the dexmedetomidine group than in the propofol group ($p=0.032$). Compared to the propofol group, scores on the Mini-Mental State Examination (MMSE) were better in the dexmedetomidine group on days three and day five ($p<0.0001$, $p=0.002$). The plasma concentrations of TNF-alpha and IL-6 were significantly increased in both groups at 12, 24, and 48 hours after surgery (all $p<0.05$), with no difference between the two groups.

Conclusion: This study of elderly patients undergoing knee replacement surgery found that post-operative delirium occurred less frequently among those anesthetized with dexmedetomidine than among those anesthetized with propofol.

Mei, B., et al. The Benefit of Dexmedetomidine on Postoperative Cognitive Function is Unrelated to the Modulation on Peripheral Inflammation. A Single-Center, Prospective, Randomized Study. *Clin J Pain.* 2020, February; 36(2): 88–95.

GASTROCNEMIUS BOTULINUM FOR PLANTAR FASCIITIS

Conservative management for plantar fasciitis (PF) includes orthotics, night splints, ice, stretching, injection with steroids and, more recently, botulinum toxin A (BTA). In 2013, a novel surgical procedure was introduced involving the release of the medial head of the gastrocnemius, with improved PF symptoms. This study assessed the efficacy of a BTA injection at the head of the gastrocnemius as a non-surgical correlate of this procedure.

Subjects were 32 patients with chronic PF. The subjects were randomly assigned to receive injections into the proximal third of the medial head with either 50 international units of BTA or a similar volume of normal saline. All injections were followed by six weeks of physiotherapy. The patients were assessed for pain using a 10-point visual analog scale (VAS) and for function with the American Orthopedic Foot and Ankle Society (AOFAS) Hindfoot Score, with assessments performed at baseline and up to 12 months following the injection.

Pain scores improved in the BTA group from an average of eight at baseline to 0.33 at one year, while pain scores in the placebo group improved from 7.8 at baseline to four at one year ($p<0.001$). Improved function at one year, as measured by the AOFAS, was also superior in the BTA group, as compared with the placebo group ($p<0.001$).

Conclusion: This study of patients with chronic plantar fasciitis found that BTA injections at the medial head of the gastrocnemius

Editor-in-Chief

David T. Burke, M.D., M.A.
Emory University, Atlanta, GA

Executive Editor

Randolph L. Roig, M.D.
Emory University, Atlanta, GA

Copy Editor

Roberta Alysoun Bell, Ph.D.
Emory University, Atlanta, GA

Assistant Copy Editor

Tracie McCargo, M.S.
Harvard Extension Sch., Cambridge, MA

Regina Bell, M.D.
Emory University, Atlanta, GA

Contributing Editors

*Benjamin Sirutis, M.D.
Dhruvil Brahmabhatt, M.D.
Joshua Elkin, M.D.
Bassem Hanalla, M.D.
Giorgio A. Negron, M.D.
Kelly Purcell, M.D.
Parth Vyasa, M.D.
Emory University, Atlanta, GA

*Michael Harbus, M.D.
Lissa Hewan-Lowe, M.D.
Icahn Sch. of Med at Mt. Sinai, N.Y., NY

*Allison Sidor Alessandra, D.O.
*Gavin Nixon, D.O.
Allen Degges, M.D.
Sadler Morrison, M.D.
LSU Health Sci. Ctr., New Orleans, LA

*Sony Issac, M.D.
Nassau Uni, East Meadow, NY

*Alexander Sheng, M.D.
Kathryn Altonji, M.D.
Kelly Brander, D.O.
Ellen Farr, M.D.
Debbie Lee, M.D.
N.W.U. /R.I.C., Chicago, IL

*Rosa Pasculli, M.D.
*Perry Zelinger, M.D.
Eytan Koch, MD
Brendan Skeehan, D.O.
Yingrong Zhu, M.D.
NYU/Rusk Inst., New York, NY

*Dr. Michael Gallaher, MD
Marielle Araujo, M.D.
Jessica Sher, M.D.
Rutgers NJMS, Newark, NJ

*Kevin Machino, D.O.
Schwab Rehab Hospital, Chicago, IL

*Steven Mann, M.D.
Sonny Ahluwalia, D.O.
Jonathan Chapekis, D.O.
Annette Lukose, M.D.
Clarisse San Juan, M.D.
Sunny Downstate, Brooklyn, NY

significantly improve pain and function.

Abbasion, M., et al. Outcomes of Ultrasound-Guided Gastrocnemius Injection with Botulinum Toxin for Chronic Plantar Fasciitis. **Foot Ankle Int.** 2020, January; 41(1): 63-68.

ALENDRONATE AND THE ROTATOR CUFF TENDON

Alendronate, a commonly used bisphosphonate, has been reported to be cytotoxic to some cells, including oral keratinocytes, gingival fibroblasts, periodontal ligament fibroblasts, and endothelial cells. As inadequate bone mineral density (BMD) has been reported as an independent determining factor of postoperative rotator cuff healing, this *in vitro* study evaluated the effect of alendronate, on rotator cuff tendon fibroblasts.

Supraspinatus tendon tissue was collected from three patients undergoing arthroscopic rotator cuff repair. From this tissue, fibroblasts were harvested and cryopreserved. The cells were then exposed to a placebo or alendronate at concentrations of 0.1 μ M, 1 μ M, 10 μ M, or 100 μ M, for one to five days. Cell viability was assessed for each group.

Cell viability was significantly decreased, in a time dependent manner, in the 100 μ M alendronate group ($p < 0.001$), reaching 25% of the total cells in five days. The decreased cell viability was mainly caused by apoptosis involving the caspase-3 pathway. In a scratch wound healing analysis, all the wounds healed well within 48 hours except the 100 μ M group ($p < 0.001$).

Conclusion: This *in vitro* study of rotator cuff tendon cells found that exposure to high concentrations of alendronate resulted in a significant reduction in cell viability.

Sung, C., et al. *In Vitro* Effects of Alendronate on Fibroblasts of the Human Rotator Cuff Tendon. **BMC Musculoskelet Disord.** 21, 19 (2020). <https://doi.org/10.1186/s12891-019-3014-1>.

EFFECT OF GRAFT CHOICE ON REVISION AFTER ACL RECONSTRUCTION

The patella tendon has previously been described as the gold standard graft for anterior cruciate ligament (ACL) repair due to its fast healing

time and reduced risk of graft rupture. However, some have identified evidence of an increased rate of injury to the contralateral, healthy ACL following this procedure. This study compared the risk of revision and contralateral ACL reconstruction between patients undergoing ACL repairs using the patella tendon and those using the hamstring tendon.

Data were obtained from the New Zealand ACL registry, a mandatory, national registry that prospectively captures data concerning patient, surgical and follow-up variables. The data includes patient demographics, data regarding surgery and follow-up evaluations using the Marx Activity Questionnaire, collected preoperatively, at six months and at years one, two and five.

The analysis included 7,155 primary ACL reconstructions. Of these, a hamstring tendon graft was used in 77.7% and a patella tendon graft in 22.3%. The crude rates of revision were 2.7% in the hamstring group and 1.3% in the patella tendon group ($p = 0.002$). In an adjusted analysis, revision was 2.51 times higher in the hamstring tendon group than in the patellar tendon group ($p < .001$). The crude rates of contralateral ACL reconstruction were 0.9% in the hamstring tendon group and 1.8% in the patellar tendon group ($p = 0.004$). In an adjusted analysis, the risk of contralateral reconstruction was 1.91 times higher in patients with a patellar tendon graft.

Conclusion: This New Zealand study of ACL reconstruction found that, compared with a hamstring tendon, those using patella tendons had a lower rate of revision, but had a greater risk of contralateral ACL repair.

Rahardja, R., et al. Effect of Graft Choice on Revision in Contralateral Anterior Cruciate Ligament Reconstruction: Results from the New Zealand ACL Registry. **Am J Sports Med.** 2020. doi: 10.1177/0363546519885148.

LONG-TERM FOLLOW-UP OF TRANSCUTANEOUS PROSTHESES

For patients with high transfemoral amputations, prosthetic fit can be challenging. One option for these patients is a surgically placed, bone anchored system. This study evaluated long-term outcomes of patients treated with these devices.

Subjects were 111 patients with unilateral transfemoral amputation

(TFA) who received the Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) implant system. This included a surgically placed intramedullary, threaded titanium fixture, an abutment (percutaneous component) press-fitted into the distal part of the fixture, and an abutment screw that connects the abutment to the fixture. The surgery occurred in two stages, six months apart. The subjects were followed using a patient-reported outcome measure, the Questionnaire for Persons with Transfemoral Amputation (Q-TFA), as well as clinical and radiographic measures.

At two, five, seven and 10 years, Q-TFA scores demonstrated significantly more prosthetic use, better motility, fewer problems and improved global situation, as compared with baseline. The survival rate of the implant was 72% at 15 years. Sixty-one patients had at least one mechanical complication, resulting in a change of the abutment and/or abutment screw.

Conclusion: This study of patients with transfemoral amputation found that these devices can improve long-term mobility, with a 15-year survival of 72%.

Hagberg, K., et al. A 15-Year Follow-Up of Transfemoral Amputees with Bone-Anchored Transcutaneous Prostheses. Mechanical Complications and Patient Reported Outcomes. **Bone Joint.** 2020; 102-B (1): 55-63.

BRAIN-DERIVED NEUROTROPHIC FACTOR AND OSTEOARTHRITIS

Recent clinical evidence supports a peripheral role of brain-derived neurotrophic factor (BDNF) in osteoarthritis (OA). BDNF acts through the tropomyosin receptor kinase B (TrkB) receptor, with data showing that synovial expression of TrkB is associated with higher OA pain. The aim of this study was to use in vitro and animal models to explore the potential contribution of knee joint BDNF/TrkB signaling to chronic OA pain.

Human OA synovium was obtained from 30 patients with knee OA, collected during total knee joint replacement surgery. Measurements were made of synovitis, messenger RNA expression of BDNF and NTRK2 (which encodes TrkB).

In a separate animal study OA was chemically created in Sprague-Dawley rats. The animals were

anaesthetized before undergoing intra-articular injection of either 100-ng/50-[micro]L BDNF (n = 6), 1-[micro]g/50-[micro]L BDNF (n = 7), 10-[micro]g/50-[micro]L BDNF (n = 7), or 50-[micro]L 0.9% saline (n = 8). Weight-bearing asymmetry and paw withdrawal thresholds were measured one and three hours after injection. A separate group of rats (n = 30) received the same injections as well as TrkB-Fc chimera (highly potent and selective for BDNF) in doses of 100-ng/50-[micro]L TrkB-Fc chimera (n = 15) or 100-ng/50-[micro]L human IgG (n = 15).

A significant positive correlation was noted between mRNA expression of NTRK2 (TrkB) and the proinflammatory chemokine fractalkine in the OA synovia. In addition, higher levels of BDNF in the synovial fluid were found in the OA group than in the controls. The blocking of BDNF with the TrkB-Fc chimera acutely reversed OA pain behavior, while intra-articular injection of BDNF further exacerbated pain responses in the rat model of OA.

Conclusion: This study suggests that inhibition of peripheral BDNF could represent an exciting new therapeutic target for the treatment of OA pain.

Gowler, P., et al. Peripheral Brain-Derived Neurotrophic Factor Contributes To Chronic Osteoarthritis Joint Pain. **Pain.** 2020, January. 61-73.

RETURN TO SPORT AFTER BILATERAL HIP ARTHROSCOPY

Several studies have reported on the return to sport after hip arthroscopy. This study assessed return to play of competitive athletes after bilateral hip arthroscopy (BHA).

Subjects included high school, college and professional athletes who were treated by BHA. Patient history was completed, including level of participation in sports within one year of the surgical date. After surgery, all underwent a structured rehabilitation protocol, with a predetermined goal of return to sport at six months from the time of the second surgery. Patient-reported outcomes were completed at a minimum of one-year post surgery.

Data were complete for 69 patients, with intraoperative findings of labral tears in over 97%. At one-year follow-up, 53.7% of the cohort had returned to their sport, including 100% of the professional athletes, 66.7% of the college athletes and 40.2% of the high school athletes. Of

those not returning to sport, 42% reported graduation (high school and college) as the reason, while 45% reported hip symptoms. Of those who did return to sport, 56% reported performance at the same ability or higher.

Conclusion: This study of athletes who underwent bilateral hip arthroscopy found that over 50% returned to sport, with over half of these returning at the same level or higher.

Rosinsky, P., et al. Rate of Return to Sport and Functional Outcomes after Bilateral Hip Arthroscopy in High-Level Athletes. **Am J Sport Med.** 2019, December ;47(14): 3444-3454.

EYE MOVEMENT AFTER SPORTS CONCUSSION

Studies of sports related concussions (SRC), using functional magnetic resonance imaging (fMRI), have noted increased activity in networks controlling eye movements, specifically the frontal eye fields and the cerebellar vermis. Studies show that the eye typically travels farther and faster during a sport-like task among those with an SRC compared with healthy controls. This may be a result of faster saccadic eye movements. Thus, increased saccade velocity (SV) is an expected abnormal outcome. This study explored the utility of smooth pursuit and saccadic eye movements in assessing SRCs.

Subjects were 18 division one athletes with an acute SRC matched with a group of 18 uninjured athletes. Using a Wii Fit soccer heading game, while wearing a head mounted monocular eye tracker, stimuli were presented on a 55-inch LED TV, with subjects asked to interact with the approaching stimulus (soccer ball). From the infrared tracker, data were used to calculate the saccadic amplitude (SA), saccadic velocity (SV), saccadic count (SC), smooth pursuit velocity (SPV) and smooth pursuit amplitude (SPA). Eye movement data were compared between groups.

Subjects in the concussion group had significantly greater SA than did matched controls (p<0.05). Those in the concussion group also had greater SV (p<0.05). The control group had a greater mean SPV than did the concussion group (p=0.019).

Conclusion: This study of concussed athletes demonstrates that during eye tracking concussed athletes experience lags in visual

pursuit that resulted in catch up saccades. This produced greater saccade velocity and amplitude than seen in controls.

Murray, N., et al. Smooth Pursuit and Saccades after Sport-Related Concussion. *J Neurotrauma*. 2020, January; 37 (2):340-346.

ANTEROLATERAL C7 TRANSFER FOR BRACHIAL PLEXUS AVULSION

Previous studies have demonstrated that the C7 nerve root has enough nerve fibers for two or more recipient nerves, and that its sacrifice on the uninjured side is usually well tolerated. This study describes a new technique for brachial plexus avulsion patients, involving bridging the C7 nerve root to the ulnar nerve and the medial antebrachial cutaneous nerve (MACN).

This retrospective study included 16 patients with a brachial plexus avulsion, who underwent surgery. In a two-stage surgery, the C7 from the unaffected side was cut and separated into its anterior and posterior divisions. The posterior division was attached to a portion of the ulnar nerve (all but the dorsal cutaneous branch), with the anterior branch of C7 attached to both, the remaining portion of the ulnar nerve (the dorsal cutaneous branch) and the MACN. After verifying connectivity by EMG, a second surgery connected the MACN, and thus restoring the damaged musculocutaneous nerve. Then, the ulnar nerve was connected to the ipsilateral median nerve restoring the function of the median nerve in the ipsilateral arm. The median interval between the two stages was 3.59 months. Strength at follow-up was measured on the five-point British Medical Research Council (MRC) grading system.

After the first surgery, five of the 16 patients noted weakness in the triceps of the donor arm, with all having recovered by five weeks. At follow-up, elbow flexion was scored as M3 in seven, M4 in four, M1-2 in four and M0 in one patient. Wrist and finger flexion were scored as M3 in seven of 16 with M0 (no movement) in two, and M1-2 in the remaining.

Conclusion: This study of 16 patients with avulsion of the brachial plexus found that a two-stage nerve graft, using C7 of the unaffected side, restored the injured arm to antigravity strength at the elbow in 10 of 16 patients, and antigravity strength at

the wrist and fingers in seven of 16. None recovered full strength.

Li, S., et al. Contralateral C7 Transfer via Both Ulnar Nerve and Medial Antebrachial Cutaneous Nerve to Repair Total Brachial Plexus Avulsion: A Preliminary Report. *Br J Neurosurg*. 2019; 33 (6): 648-654.

DIRECT CURRENT STIMULATION AND PHYSICAL THERAPY FOR STROKE

Studies involving transcranial direct current stimulation (tDCS) have demonstrated that this technique can reduce interhemispheric inhibition, and improve regional cerebral blood flow after a stroke. Most of these studies have involved patients with chronic stroke. This randomized, triple blind, sham-controlled study examined the effects of tDCS in patients with an acute stroke.

Subjects were 18 and 80 years of age hospitalized for an acute stroke. The patients were randomized to receive intensive physiotherapy and occupational therapy two hours per day, with either anodal tDCS (a-tDCS; 1 mA for 20 minutes) or sham tDCS. The a-tDCS was provided with the anode placed over the primary motor cortex of the lesioned side. Treatment onset was at 48 hours post onset. The primary outcome measure was the Wolf Motor Function Test (WMFT), with secondary outcomes including a variety of measures of physical and affective outcome. Follow-up measures were recorded at 48 hours post stroke (T0), weekly for one month, and at three, six and 12 months.

Both groups demonstrated significant improvement in WMFT scores. Beginning at four weeks, the tDCS group showed significantly better scores than the sham group, ($p=0.04$) with the difference maintained at one year ($p=0.02$). From the third week forward the treatment group was also found to have better improvement in the Hospital Anxiety and Depression Scale. Most patients noted a slight tingling or itching with 40% noting a burning sensation. None requested discontinuation of the session or withdrawal from the study.

Conclusion: This prospective blinded study of patients with acute stroke found that transcranial direct current stimulation, delivered during acute rehabilitation, could significantly improve motor function and mood, with results lasting up to one year.

Bornheim, S., et al. Transcranial Direct Current Stimulation Associated with Physical Therapy in Acute Stroke Patients—A Randomized, Triple Blind, Sham Controlled Study. *Brain Stim*. 2020, March-April;13(2):329-336.

UBROGEPANT FOR MIGRAINE

Calcitonin gene-related peptide (CGRP) is a neurotransmitter expressed in peripheral sensory trigeminal nerves that innervate the pain sensitive dura and the blood vessels of the meninges. Ubrogepant is an oral, small molecule CGRP receptor antagonist which has been found to be effective for the treatment of migraine headaches. This placebo-controlled study compared the efficacy of two doses of ubrogepant for the treatment of acute migraine.

Subjects were adults 18 to 75 years of age, with at least a one-year history of migraine, with or without aura. The subjects were randomized to receive one of three identical tablets including a placebo, ubrogepant, 50 mg, or ubrogepant, 100 mg, to be ingested at the onset of a migraine. The participants rated headache severity and non-headache symptoms associated with migraine, including photophobia, phonophobia, nausea and vomiting for up to 48 hours.

Data were completed for 485 in the placebo group, 466 in the 50 mg ubrogepant group and 485 in the 100 mg ubrogepant group. Freedom from pain at two hours was reported in 11.8% of the placebo group, 19.2% of the 50 mg group ($p=0.002$) and 21.2% of the 100 mg group ($p<0.0001$). Freedom from the most bothersome symptom at two hours was reported in 27.8% of the placebo group, 38.6% of the 50 mg group ($p=0.002$) and 37.7% of the 100 mg group ($p=0.002$).

Conclusion: This randomized, double-blind, placebo-controlled trial of patients with acute migraine found that treatment with ubrogepant increased the chance of freedom from headache pain at two hours.

Dodick, D., et al. Ubrogepant for the Treatment of Migraine. *N Engl J Med*: 2019, December 5;381(23): 2230-2241.

CRANIOSACRAL THERAPY FOR CHRONIC PAIN

Among complementary therapies for the treatment of chronic pain disorders, craniosacral therapy (CST)

has been used for the treatment of patients complaining of pain in the back and neck, headache and migraine. Derived from osteopathic manipulation techniques, the specific mechanisms of CST have not been well studied. This literature review and meta-analysis was designed to better understand the effect of CST in patients with painful conditions.

Medical literature was searched through August 2018 for randomized controlled trials or randomized crossover trials that included treatment of nonmalignant pain. The primary outcome measures were pain intensity and functional disability. Secondary outcomes included physical quality of life, mental quality of life, global impairment and safety. From the studies identified, 10 randomized controlled trials were included in the analysis.

For the pooled effect on pain intensity, compared with treatment as usual, CST resulted in significant small to medium size pooled effects, noted directly after the end of the intervention for: pain intensity ($p=0.005$), functional disability ($p=0.002$), physical quality of life ($p=0.04$), and global improvement ($p=0.002$). No serious adverse events were reported.

Conclusion: This systematic review of randomized controlled trials found that craniosacral therapy produced statistically significant and clinically small to medium improvement in pain, function and quality of life.

Haller, H., et al. Craniosacral Therapy for Chronic Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials. **BMC Musculoskeletal Disorders**. 21, 1 (2020). <https://doi.org/10.1186/s12891-019-3017-y>.

METHYLPHENIDATE AND COGNITION AFTER BRAIN INJURY

Cognitive impairment is one of the most common and disabling sequelae of traumatic brain injury (TBI). Some guidelines recommend methylphenidate for the treatment of postinjury deficits, including attention and processing speed. This literature review was completed to determine the effect of methylphenidate as a treatment for brain injury.

A literature review was conducted for studies published between 1980 and December of 2017. The selected studies included adult patients, diagnosed with acquired brain injury and treated with methylphenidate,

with at least one measure of cognitive function administered. Of the 11 selected, seven were randomized controlled trials, two were pre-post trials, one was a prospective controlled trial, and one was a case study.

Across the domains of working memory, processing speed and/or attention, 10 studies reported statistically significant improvements. No studies reported a worsening of performance on cognitive measures with the drug treatment.

Conclusion: This literature review of studies of patients with acquired brain injury found Level 1A evidence that methylphenidate can improve cognitive abilities, particularly working memory, processing speed and attention.

Barnett, M., et al. Effectiveness of Methylphenidate in Improving Cognition after Brain Injury in Adults: A Systematic Review. **Brain Inj**. 2020; January 34(1): 1-10.

POSTOPERATIVE DELIRIUM AND NEUROFILAMENT LIGHT

Delirium is characterized by inattention and cognitive failure, often as a physiologic consequence of a medical or surgical condition. Evidence shows that delirium can herald the onset of dementia, as it reveals underlying neurodegeneration in the presence of an acute stressor. This study explored whether the neuromarker, plasma neurofilament light (NFL), is associated with MRI markers of neurodegeneration, and whether postoperative delirium is associated with a rise in NFL levels.

Subjects were 108 adult patients scheduled for major, elective, non-intracranial, non-cardiac surgery. The participants underwent blood draws preoperatively and on each of the first four post-operative days for markers of inflammation (cytokines) and NFL. All were scanned with a 3 Tesla whole body MRI scanner, with white matter injury quantified with diffusion tensor imaging (DTI). Delirium assessments were made using the Confusion Assessment Method (CAM), with delirium severity assessed with the Delirium Rating Scale-8 (DRS). The data were reviewed for the association between NFL changes and delirium.

Delirium occurred in 39 of the 108 patients (36.1%). In all subjects, NFL levels rose on post-operative day one, with the rise more profound in the delirious group ($p<0.001$). This rise in NFL relationship showed dose-

dependence, such that NFL rose proportionately to delirium severity ($p<0.001$). The rise in interleukin-8 was significantly related to delirium severity on day one ($p<0.001$), while the cytokines, interleukin-1 beta and interleukin-10, were significantly related to NFL, but not to delirium severity. The association between the rise in NFL and delirium severity was independent of changes in inflammatory burden ($p=0.038$).

Conclusion: This study of patients undergoing elective surgery found that post-operative delirium is associated with increases in the biomarker neurofilament light, with the relationship independent of changes in inflammation.

Casey, C., et al. Postoperative Delirium Is Associated with Increased Plasma Neurofilament Light. **Brain**. 2020, January; (143); 47-54.

RED MEAT CONSUMPTION AND MORTALITY

While previous studies have suggested an increased risk for cardiometabolic disease with increased consumption of red meat and processed red meat, methodological limitations of previous studies have tarnished subsequent conclusions. This literature review and meta-analysis was designed to better understand the association between red meat consumption and all-cause mortality, cardiometabolic outcomes, quality of life and satisfaction with diet among adults.

Medical literature was reviewed for cohort studies which enrolled at least 1,000 subjects and compared participants consuming different amounts of unprocessed red meat or processed red meat. Processed red meat was defined as mammalian meat, with processed red meat classified as white or red meat preserved by smoking, curing, salting or adding chemical compounds. Separate analyses were completed for unprocessed red meat, processed meat and mixed red meat.

Data for the quantitative analysis included 71 reports of 55 cohorts, for a total of 4.2 million participants. A reduction in the consumption of unprocessed red meat/processed red meat by three servings per week was associated with a very small reduction in the risk for all-cause mortality (RR=0.92/0.93) cardiovascular mortality (RR=0.90/0.90), stroke (RR=0.94/0.94), myocardial infarction (RR=0.94/0.93) and type two

diabetes (RR=0.78/0.90). The authors note that the magnitude of absolute effect, if indeed it exists, is very small, and the certainty of the evidence is low.

Conclusion: This literature review and meta-analysis found a very small association between red meat and processed red meat consumption and cardiovascular and cerebrovascular outcomes. The authors note that the causal relationship is not clear.

Zeraatkar, D., et al. Red and Processed Meat Consumption and Risk for All-Cause Mortality and Cardiometabolic Outcomes: A Systematic Review and Meta-analysis of Cohort Studies. *Ann Intern Med.* 2019, November; 171 (10): 703-710.

NEUROTOXICITY OF ANTIBODIES IN CANCER THERAPY

Pharmacological antibodies are engineered to bind a target and promote a specific function. In anticancer therapy, these targets can include cell surface receptors or soluble proteins. This study summarized the neurotoxicity profile of antibodies in cancer pharmacotherapy, in order to better understand their neurologic side effects.

This literature review included articles published from November 2010 to August 2018. The search focused upon classes of monoclonal antibodies, including Bi-specific T-cell engager (BiTE), anti-CD20, anti-CD30, anti-CD52, anti-cytotoxic T-lymphocyte-associated antigen-4 (CTL-4), anti-epidermal growth factor receptor (EGFR), anti-human epidermal growth factor receptor (HER), anti-programed death ligand-1 (PDL-1), anti-program cell death protein 1 (PD-1) and anti-vascular endothelial growth factor (VEGF). The literature search located 54 articles for analysis. Side effects were addressed and summarized.

The most common side effects of blinatumomab (Anti CD3 and CD19 for hematologic cancers) were headaches (38%), encephalopathy (17%) and tremor (17%). For the anti-CD20 drugs (for the treatment of hematologic cancers) the most common side effects were headaches (15%) and neuropathy (11%). The most common side effects of Brentuximab (antibody targeting CD30) were neuropathy (57%) and headache (18%). Grade 3–4 neuropathy was reported at a frequency of 11%. For Alemtuzumab

(active at CD52) peripheral neuropathy was reported (5–15%), myelitis (3%), and optic neuritis (2%). For anti-CTL4 medications such as Ipilimumab, the most common side effect was headache requiring hospitalization (0.7%). For anti EGFR medications the most common side effects were headache (25%), neuropathy (16%) and sleep disorders (15%). For antibodies targeting HER2, neuropathy was reported at a frequency of 33%, myalgia/ myopathy in 26%, headache in 16% and grade 3–4 neuropathy in 3%. For anti-PD-1 medications, the most common side effect was headache (3%). For anti-VEGF, headache was reported at a frequency of 25%.

Conclusion: This study of new cancer pharmacotherapy found that monoclonal antibody associated neurotoxicity in cancer is not rare and should be expected.

Horta, E., et al. Neurotoxicity of Antibodies in Cancer Therapy: A Review. *Clin Neurol Neurosurg.* 2020, January: 188.105566.

TRANSCRANIAL DIRECT CURRENT STIMULATION FOR LOW BACK PAIN

Chronic low back pain (CLBP) is a common disorder, often resistant to effective treatment strategies. Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique, shown to be effective in treating patients with various pain disorders. This study evaluated the efficacy of tDCS on pain intensity among patients with CLBP.

This prospective, double-blind, randomized, sham controlled study recruited patients, 18 to 65 years of age, with nonspecific CLBP. All subjects received 20 minutes of either real or sham tDCS. Pain intensity was measured before and after treatment by a numerical rating scale (NRS), with muscle activity assessed by surface electromyography (sEMG). For both groups, the dry anode electrode was placed over C3/C4 and the cathode over M1. The active tDCS was applied at a constant current of 2mA, delivered for 20 minutes.

Data were gathered for 26 patients in the tDCS group and 25 in the sham tDCS group. NRS scores decreased from 5.1 to 3.3 in the tDCS group ($p<0.000$) and from 4.6 to 4.4 in the sham group ($p=0.670$). After the treatment session, pain relief was demonstrated in 17 of 26 in the tDCS

group, and in eight of 25 in the sham group. EMG data revealed no difference between groups.

Conclusion: This study of patients with chronic low back pain found that a single episode of transcranial direct current stimulation can reduce back pain severity.

Jiang, N., et al. Effect of Dry Electrode Based Transcranial Direct Current Stimulation on Chronic Low Back Pain and Low Back Muscle Activities: A Double-Blind, Sham Controlled Study. *Restor Neurol Neurosci.* 2020. Pre-press. 10.3233/RNN-190922.

LOW-DOSE STATINS AND STROKE SEVERITY

Stroke is the leading cause of death and disability in China. Previous studies have demonstrated that statin treatment is associated with lower stroke severity and better functional outcome among adults. Cardiovascular studies have also shown that statins exert anti-inflammatory, cholesterol-lowering and cardiovascular protective effects. This retrospective study analyzed the association between pre-stroke use of low-dose statins and the severity of an initial stroke.

Subjects were consecutive patients with acute, ischemic stroke, hospitalized between May of 2011 and January of 2017. Baseline data included labs, vital signs, statin use, stroke severity based upon the National Institutes of Health Stroke Scale, and the functional outcome at 90 days post-discharge based on the modified Rankin scale (mRS) score. The patients were followed for 90 days after discharge, with the primary outcome variables including stroke severity and mRS. The primary endpoints were stroke severity on admission and functional outcomes at 90 days.

Subjects were 1,878 patients, of whom 121 (6.4%) had used statins before the stroke. The reasons for this use included hypertriglyceridemia ($n=22$), prevention of coronary heart disease ($n=90$), atherosclerosis with arterial stenosis and occlusion ($n=5$), rheumatic heart disease and a-fib ($n=4$).

Admission NIHSS scores were significantly lower among patients who were taking statins before the stroke than among those who were not ($p<0.001$). The statin group also had better mRS scores at 90 days ($p=0.007$). In a subgroup who initiated statin therapies soon after stroke, better functional outcomes

were noted than among those who initiated statins late after stroke ($p < 0.05$).

Conclusion: This study demonstrates that low-dose statins, taken prior to the onset of an ischemic stroke, are associated with reduced stroke severity upon hospital admission.

Dong, S., et al. Low-Dose Statin Pretreatment Reduces Stroke Severity and Improves Functional Outcomes. *J Neurol*. 2019, December; 266(12): 2970-2978.

DYNAMIC ULTRASOUND IN ANTERIOR CRUCIATE LIGAMENT TEARS

For diagnosing complete anterior cruciate ligament (ACL) tears, an MRI has been found to have a sensitivity of 87% and a specificity of 93%. When diagnosing partial tears, the sensitivity is much less. This study assessed the efficacy of dynamic high-resolution ultrasound (US) imaging of the knee for diagnosing ACL tears.

Subjects were adult patients who underwent arthroscopy and at least one preoperative US with an 8-12 MHz broadband linear array transducer. The findings of this ultrasound were compared with findings during arthroscopic surgery.

Of the 247 patients evaluated, 120 knees showed evidence of ACL tears during US examination, with 60 described as partial and 59 as complete tears. At arthroscopic surgery, 108 ACL tears were found, of which 60 were partial, and 48 were complete tears. Sensitivity of US for the detection of complete ACL tears was 79%, with a specificity of 89%, a positive predictive value (PPV) of 63%, and a negative predictive value (NPV) of 95%. Partial ACL tears were correctly identified with a sensitivity of 52%, specificity 85%, a PPV of 52% and an NPV 84%.

Conclusion: This retrospective study of patients undergoing arthroscopic surgery found that ultrasound may be useful in diagnosing ACL tears, with a higher sensitivity for complete ACL tears than for partial ACL tears.

Breakers, M., et al. Diagnostic Accuracy of Dynamic Ultrasound Imaging in Partial and Complete Anterior Cruciate Ligament Tears: A Prospective Study in 247 Patients. *BMJ Open Sport Exerc Med*. 2019.5(1): e000605.

TREADMILL TRAINING FOR CHARCOT-MARIE-TOOTH

Charcot-Marie-Tooth neuropathy is the most common inherited neurologic disorder. While positive effects have been noted with aerobic training, treadmill training has never been tested in this disease.

This study evaluated the efficacy and safety of structured treadmill training for patients with Charcot-Marie-Tooth 1A (CMT1A).

This multicenter, prospective, randomized, single-blind, controlled study included 53 patients with a confirmed diagnosis of CMT1A. Both groups were seen twice per week for 12 weeks, with both groups receiving stretching and proprioceptive exercises. In addition, the treatment group underwent two, 30-minute sessions of treadmill training, with effort titrated up to 70% of the maximum load. All participants were evaluated after three and six months of treatment. The primary outcome measures were the six-minute walk test and a 10-minute walk test.

Most of the patients demonstrated improvement on at least one of the primary measures at three and six months, without significant difference between the two groups. On the six-minute walk test, similar improvements were seen between the groups at three months, while further improvement was noted at six months on the 10-minute walk test, with no significant difference between the two groups.

Conclusion: This study of patients with the most common variant of Charcot-Marie-Tooth found that stretching and proprioceptive exercises could improve the patients' function with no additional benefit found when adding treadmill training.

Mori, L., et al. Treadmill Training in Patients Affected by Charcot-Marie-Tooth Neuropathy: Results of a Multicenter, Prospective, Randomized, Single-Blind, Controlled Study. *Euro J Neurol*. 2020;27 (2): 280-287.

HIGH INTENSITY AEROBIC EXERCISE AND BRAIN DERIVED NEUROTROPHIC FACTOR

Mild cognitive impairment (MCI), is considered a clinical prodrome of Alzheimer's disease (AD) and other dementia. Brain derived neurotrophic factor (BDNF), plays a predominant role in neuroplasticity and has been shown to decrease progressively with age. As studies have shown a positive effect on

cognitive performance following acute exercise, this study assessed the effect of acute exercise on BDNF.

Subjects were adult patients with a diagnosis of amnesic MCI, randomized into an exercise group ($n=35$) or a control group ($n=29$). Several cognitive performance tests were administered at baseline and after an exercise protocol. Participants performed a graded exercise protocol to volitional exhaustion involving a three-minute warm-up of unloaded cycling followed by an incremental phase during which the load increased by 25 watts every two minutes until the test was self-terminated. Serum BDNF (sBDNF) was drawn at baseline and after the exercise protocol.

The sBDNF concentration increased in the exercise group a baseline median of 4564.61 pg/mL1 to 5173.27 pg/mL1 at follow up. The levels decreased in the resting control group from 4593.74 pg/mL1 to 3974.66 pg/mL1 ($p=0.024$). However, the control group made fewer errors on the sustained attention task (SART) compared with the exercise group ($p=0.025$). Measures of visuospatial learning and memory or executive function did not change significantly between groups.

Conclusion: This study indicates that a single session of high-intensity exercise in patients diagnosed with mild cognitive impairment can enhance levels of circulating brain derived neurotrophic factor but does not improve visual-spatial learning and memory, sustained attention, and executive function.

Devenney, K., et al. Acute High Intensity Aerobic Exercise Affects Brain Derived Neurotrophic Factor in Mild Cognitive Impairment: Randomized Controlled Study. *BMJ Open Sport Exerc Med*. 2019;5: e000499. doi:10.1136/ bmjsem-2018-000499.

MICROFRACTURE AT THE TALUS

Osteochondral lesions of the talus (OLT) may have symptoms such as swelling and locking sensation with deep ankle pain. As conservative treatments are frequently effective, arthroscopic microfracture may be recommended. This study evaluated the long-term functional outcomes of arthroscopic microfracture for OLT.

Subjects were consecutive patients, 18-60 years of age with OLT who had failed non-operative treatment, and subsequently underwent microfracture surgery. All were assessed at baseline and follow

(Continued from page 2)

Nicole Katz, M.D.
Mia Song, D.O.
Temple University, Philadelphia, PA

*Shane Davis, M.D.
Michael Beckman, M.D.
Jeff J. Kim, M.D.
Gabriel Sanchez, M.D.
Ryan Turchi, M.D.
University of California/Irvine, CA

*Andrew Minkley, M.D.
Ashley Eaves, M.D.
University of Washington, Seattle, WA

*Adem Akatas, D.O.
*Michael Krill, M.D.
James Cole, M.D.
Washington Univ., St. Louis, MO

Executive Editor Emeritus
Donald F. Langenbeck, Jr., M.D.

Subscription Manager
Michael P. Burke, M.S.

***Regional Managing Editors have attested that they have no financial conflict of interest when choosing articles that appear in Rehab in Review.**

-up with the Foot and Ankle Outcome Score (FAOS) a Visual Analog Scale (VAS) for pain and a 36 item Short Form Health Survey (SF-36). X-rays of the ankle were taken preoperatively and at one, three, six and 12 months postoperatively and then annually.

Follow-up data were completed for 165 ankles at a mean of 6.7 years. The VAS pain scores improved from 6.2 preoperatively to 1.7 postoperatively ($p < 0.001$). Significant improvements were also noted in the SF 36 ($p < 0.001$) and the FAOS ($p < 0.001$). While body mass index, age and lesion size were not related to functional outcomes, symptom duration was found to be negatively correlated with FAOS improvement.

Conclusion: This study of patients with recalcitrant osteochondral lesions of the talus found that microfracture could be effective in reducing pain at up to 6.7 years.

Choi, S., et al. Arthroscopic Microfracture for Osteochondral Lesions of the Talus: Functional Outcomes at a Mean of 6.7 Years in 165 Consecutive Ankles. **Am J Sports Med.** 2020, January; 48 (1): 153-158.

Rehab in Review (RIR) is produced monthly by physicians in the field of Physical Medicine and Rehabilitation (PM&R), with the cooperation and assistance of Emory University School of Medicine, Department of Rehabilitation Medicine. The summaries appearing in this publication are intended as an aid in reviewing the broad base of literature relevant to this field. These summaries are not intended for use as the sole basis for clinical treatment, or as a substitute for the reading of the original research.

The Emory University School of Medicine designates this journal based activity for a maximum of 3 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity. The Emory University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians. The journals are offered as a CME accredited activity for 3 years from the date of original publication.

RIR is affiliated with the Association of Academic Physiatrists, the World Health Organization, and the Chinese and Indian Societies of PM&R and endorsed by the International Society of Physical and Rehabilitation Medicine.

Private subscriptions are available by email at rehabinreview@aol.com or by fax or phone at (417) 779-9101.
ISSN # 1081-1303



REHAB IN REVIEW

Produced by the Department of
Rehabilitation Medicine, Emory
University School of Medicine



EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Department of
Rehabilitation
Medicine

Expanding the frontier of rehabilitation sciences in research, teaching, and patient care