Sports Concussion and the Clinical Neurologist, Part III

The third and final installment in a series on sports concussion explores treatment and the role of the neurologist.

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When considering the role of the neurologist in the management of the concussed athlete we must first realize that we are coming in late in the game. The reality is that due to the shear number of concussions and the fact that most concussion symptoms are short lived, it is logistically impossible for every concussed athlete to be seen by a neurologist. Furthermore, until recently neurologists and more specifically the American Academy of Neurology have not been active in sports concussion management, often deferring to other specialties. This happens despite dealing with all associated concussion symptoms on a daily basis in clinical practice and having significant exposure to the common tools used to evaluate the concussed athlete, i.e. neuropsychological testing, neuro-imaging, electrophysiological, and vestibular testing. The role of the neurologist, especially in the community setting, has and will likely remain as a consultant for patients with prolonged headache, vestibular, and neurocognitive issues. These patients require more involved treatment, which may include additional education, academic and work related accommodations, physical/vestibular therapy, cognitive rehabilitation, psychotherapy, and pharmacological treatment.

Concussion symptoms tend to be short lived and last between 10 and 14 days and therefore usually do not require treatment. [54, 55] The one exception is headache, which tends to be present from the onset. Headache, depression, and sleep disturbances are the most common symptoms requiring pharmacological management. Vertigo/disequilibrium and musculoskeletal pain are best treated with physical medicine.

When it comes to the pharmacological management of the concussed athlete there are little to no evidenced based-studies. (Conidi, poster International Headache Society Annual Meeting, 2011). A majority of the management is based on consensus opinion, a few case reports, and the clinical experience of the treating physician, who will often rely on principals used in the management of non-concussed patients. For example, medications should be easily titrated and weaned, and used at the lowest effective dose. Attempt to use one medication to treat multiple symptoms, i.e. headache and/or sleep disturbances and/or depression. The most important principal that the neurologist must realize is that shortening the duration of symptoms can have catastrophic effects as medications can mask unresolved concussion symptoms. Pharmacological treatment is not routinely recommended unless the athlete is suffering from prolonged disabling symptoms. Furthermore, prophylactic medications need to be discontinued and the athlete monitored off of all such medications for sufficient time so that the medication is completely out of their system (one week is common) before any return to play decisions are made. Finally, pharmacologic treatment of elite professional and elite amateur athletes needs to take into account governing bodies rules and regulations for banned substances and one should always check with the governing body to see if the medication is allowed. Most governing bodies including the NHL use the World Anti-Doping Associations (WADA) guidelines, which

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are the strictest. The National Football League (NFL) and Major League Baseball (MLB) have their own guidelines. All of the above guidelines are very similar and include such substances and anabolic steroids, amphetamines and other stimulants, glucocorticoids, beta agonists, beta blockers, peptide hormones and growth factors, hormone antagonists and modulators (i.e. masking agents), diuretics and other masking agents, blood/oxygen transport enhancers, narcotics, and cannabinoids. A number of which are routinely used by the neurologist to treat symptoms especially headache.

Depression. Depression is a common and often unrecognized symptom of concussion. Behavioral therapy is the mainstay in treatment of depression; antidepressants should be reserved for the most chronic and refractory cases. Tricyclic antidepressants (TCAs) including amitriptyline and nortriptyline are usually used as first line therapy and are also effective in the prevention of headache. In addition, they have sedative properties, making them effective sleep agents, and titration and weaning schedules are much shorter than for SSRIs and SNRIs. Bupropion HCL (Wellbutrin) is an option in patients with prolonged significant daytime fatigue, decreased energy, and in patients with significant issues with attention and concentration, as it is often used off label for AD/HD. The medication has the potential to lower seizure threshold and should be avoided in patients with structural abnormalities on MRI or epileptic activity on EEG. SSRIs/NRIs should be avoided secondary to prolonged titration and weaning schedules. They can also be sedating and have a higher risk of suicide in adolescents and late teens. If an SSRI/NRI needs to be considered, such as a patient with prolonged symptoms and who has failed TCAs, venlafexine (Effexor) would be the preferred drug, as it has stimulating properties and has been shown to be effective as a migraine preventative. MAO inhibitors should also be avoided due to drug interactions, especially with anti-migraine medications. Finally, Strattera (atomoxetine), which is FDA approved for the treatment of ADD, could be considered if there is significant trouble with attention and concentration.

Sleep. Sleep is best treated with natural, over the counter remedies to prevent dependency and rebound insomnia. Compounds such as diphenhydramine (25 to 50mg), valerian root and melatonin (3-12mg) can be used alone or in combination. Diphenhydramine is also effective in aborting migraine and other headaches and can also be used as a short-term headache preventative. Melatonin acts to maintain sleep. If medication is required, then TCAs would be considered first line due to their ability to treat associated symptoms. Trazodone, which is chemically similar to TCAs, is another alternative. Sedative hypnotics such as zolpidem (Ambien) and eszopiclone (Lunesta), which can cause rebound insomnia and worsen post concussion symptoms of headache, cognitive symptoms, or dizziness, should be avoided as should benzodiazepines and barbiturates.

Headache. Headache is the most common symptom of sports-related concussion, occurring in up to 88 percent of all sports-related concussions. Most patients fall under the International Headache Society classification of acute post traumatic migraine. Exacerbation of primary headaches such as tension headache, cervicogenic headache, and even cluster headache can occur alone or in combination. Just as with other primary headache disorders, treatment involves abortive and prophylactic therapy, however most patients do not develop chronic post-traumatic migraine and only require abortive medication. As with other forms of migraine, abortive treatment should be instituted when the pain is mild and headache should be treated completely. Over the counter medications including acetaminophen and NSAIDs usually would have been tried before the patient comes to the attention of a neurologist. In these patients triptan medications would be the next logical choice. If the patient does not respond consistently, the triptan can be combined with an over the counter NSAID such as naproxen. In patients where the headache develops rapidly or in patients that wake up with a headache, nasal and/or injection is usually more effective because oral medications may not be readily absorbed secondary to the development of gastroparesis late in the headache process. Dihydroergotamine (DHE-45, Migranal) are excellent alternatives for triptan non-responders, as is ketorolac (Toradol) PO or IM, which can be added to triptans or DHE-45 or used alone in patients who have contraindications to the use of the above medications. With any headache type, narcotics and butalbital/caffeine containing compounds should never be used because of their minimal effects on the hypothesized neurovascular process involved in post-traumatic migraine and are the main culprits in triggering medication overuse headache. Patients who continue to experience post-traumatic migraine headache for more than a month, and at a frequency of greater than six to eight headaches per month, may benefit from prophylactic treatment.

Similar to sleep, the mainstay of treatment is the TCAs; they also treat associated symptoms. Anti-epileptic medications (AEDs) which are the mainstay of preventative migraine treatment for most neurologists, are not good options in

TABLE 1. ZURICH GRADED RTP		
Rehabilitation Stage	**Functional Exercise at each stage**	**Objective of each stage**
1. No Activity	Complete physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming, stationary bike	HR to 70%
3. Sport specific exercise	Skating, running drills without contact	Add movement
4. Non contact training	Complex drills without contact	Exercise, coordination and cognitive load
5. Full Contact	Normal practice and training	Restore confidence and simulate game sit.
6. Return to Play	Game Play	

concussed patients with headache as they all can cause sedation which concussed athletes already experience, and require somewhat prolonged titration schedule and weaning schedules. Furthermore, topiramate (Topamax), a widely prescribed preventative migraine medication, can cause unwanted weight loss and worsen psychomotor retardation, which is a common associated symptom in athletes with prolonged concussion symptoms. Another common AED used in headache prevention is valproic acid (Depakote). Weight gain and hair loss are common side effects with this medication, the latter of which can be a significant issue in elite and professional athletes, especially females, who often have lucrative endorsement contracts which are based at least in part on their physical appearance. If the neurologist is going to consider using an AED, zonisimide (Zonegran) 50 to 100mg bid is an option. Beta blockers and calcium channel blockers should be avoided. Both can cause a significant decrease in pulse rate, which in conditioned athletes with low resting pulse rates can cause syncope. Furthermore, and as mentioned previously, beta blockers are on a majority of the banned substance lists and can increase the lethargy that athletes already experience. Other options include leukotriene receptor antagonists, i.e. monoleukast (Singulair) and zafirlukast (Accolate). These options are hypothesized to inhibit the neurovascular inflammatory response. They have minimal side effects, along with a proven safety record in children, but their efficacy has not been demonstrated in Class I trials. Another interesting possibility is memantine. The drug has been shown in retrospective studies to be an effective migraine prophylactic.[56] The drug is an NMDA receptor antagonist and appears to inhibit cortical spreading and depression, seen both in concussion and migraine. It may also be protective and improve associated concussion symptoms. Finally, there is class one evidence that certain vitamins including; magnesium oxide 200-400 mg per day, whole leaf feverfew, riboflavin, and Petadolex (petasites root) alone or in combination are effective in preventing migraine. And natural/holistic therapy is favored by athletes, as they have no significant side effects or banned substance issues.

Approximately 15 percent of patients will go on to develop chronic post-traumatic headache (attributed to mild head injury). (Conidi, Poster International Headache Society Meeting, Berlin, June 2011). The FDA has recently approved onabotulinum toxin type A (Botox) for the treatment of chronic migraine. This medication should be avoided due to its prolonged duration of action, roughly three months, meaning it would preclude an athlete from returning to play for three months, because even if asymptomatic, the toxin could be masking unresolved concussion symptoms. As is the case with other forms of chronic headache, patients who experience prolonged headache after concussion require a multi-disciplinary approach and are best referred to a tertiary headache center/headache specialist.

Finally, a significant role for the neurologist may be in answering one of the dilemmas facing sports concussion management. In athletes whose daily headache is the only remaining symptom, the question arises: Is the headache a continuation of the concussion? Or has the patient developed chronic post-traumatic migraine or other primary headache disorder?

RETURN TO PLAY

There have been a number of guidelines published to assist physicians and other clinicians in determining the readiness of athletes to return to play (RTP) after sports concussion. These include: The Cantu Guidelines (1986), which have been adopted by the American College of Sports Medicine, Colorado Medical Guidelines (1991) which were the basis for the 1997 AAN guidelines and have been adopted by the National Collegiate Athletic Association (NCAA), The American Academy of Neurology Guidelines (1997), International guidelines from Vienna 2001, Prague 2004, and Zurich 2008.

It is extremely important that the physician involved in returning an athlete to play understand that all current RTP guidelines are based almost solely on consensus opinion and not evidence based studies. In addition, the AAN guidelines should not be used: They rely on an outdated grading system which is based on loss of consciousness, an event occurring in less than 10 percent of all athletes and allows for the same day return to play. The AAN is currently updating the guidelines to be the most evidenced based to date and are scheduled for release in the spring of 2012. In addition, in an attempt to bridge the gap the AAN released a position statement (Alessi,

Conidi, Kutcher) in late 2010 (See previous installments). Before an athlete can be considered for return to play they must be completely asymptomatic, off of all medications, with a normal neurological exam, and all pre-concussion testing returned to baseline. The most widely used RTP guidelines are Zurich 2008 (See Table 1). The most important aspect of the statement is that no athlete should return to play on the same day they have sustained a concussion. Furthermore, return to play protocol following a concussion follows a stepwise process based on a full clinical and cognitive recovery before the athlete is allowed to return to play. With this stepwise progression, the athlete should continue to proceed to the next level if asymptomatic at the current level. Each step should take 24 hours so that an athlete would take approximately one week to proceed through the full rehabilitation protocol. If any post concussion symptoms occur while in the stepwise program, the patient should drop back to the previous asymptomatic level and try to progress again after a further 24-hour period of rest has passed.

Elite and Professional Athletes. RTP guidelines should not be any different no matter what level the athlete. External and financial influences should never play a role in RTP. A league sponsored study demonstrated that NFL players may recover quicker than younger players, however this data has not been duplicated.[57] Given the possibility of external influences, the NFL, after a recent Congressional investigation, has agreed that RTP should be made after consultation and agreement by both a team neurologist and independent consulting neurologist.

High School Athletes and Children. Researchers have demonstrated that children age 10 and younger and high school athletes recover more slowly. [58] Young children report different concussion symptoms and require age appropriate symptom checklists and significant parental input. The developing brain has a more complex neurochemical and neuroanatomical make up, and studies have demonstrated that the complex physiological changes that occur with concussion take longer to resolve. [58] Neuropsychological testing needs to be age matched; computerized testing has not been validated and therefore may not be appropriate in younger children. The mainstay of treatment in children has been what is termed "cognitive rest." This entails a child limiting exertion with activities of daily living and limiting scholastic and other cognitive stressors such as text messaging, videogames, etc. while symptomatic.[59-61] Recent studies, however, have shown that in children with prolonged concussion symptoms a protocol of activity to tolerance may be beneficial.[62-64] Given that current pathophysiological and MRI spectroscopic studies are demonstrating changes in brain metabolism lasting upwards of 30 days, [47] there need to be longer periods between graded exertion, and this author recommends at least three days between the steps outlined in Zurich 2008.

LONG TERM EFFECTS

Neuropathological Changes. In 1928 Martland published a paper in the Journal of the *American Medical Association* entitled "punch drunk." In it he described a group of what he termed "poor fighters" who tended to "take considerable head punishment." According to the author, early symptoms included occasional clumsiness, slight ataxia, and periods of confusion. He noted that many never progress beyond this stage while others would go on to develop tremors, dysarthria, deafness, physical slowing, "dragging legs while walking" and mental deterioration to a point where some required institutionalization. Some would go on to develop a progressive neurological syndrome leading to mental or physical helplessness.[78] In 1937 Millspaugh, in describing effects in Navy boxers, coined the term dementia pugilistica.[77] The term Chronic Traumatic Encephalopathy CTC first appeared in the literature in the mid 1960s, and in 1973 Corsellis, Bruton, and Freeman-Browne described three stages of clinical deterioration in CTE. [65] (See Table 2) Pathologically CTE is defined by reduction in brain weight, enlargement of the lateral and third ventricles, thinning of the corpus callosum, cavum septum pellucidum with fenestrations, scarring and neuronal loss of the cerebellar tonsils, and atrophy of the frontal, temporal and parietal lobes.[65] Microscopically CTE involves neuronal loss and gliosis throughout the brain including the hippocampus, amygdale, thalamus, substantia nigra and cerebral cortex.[65-67] With the neurofibrillary degeneration of CTE, Tau immunoreactive neurofibrillary (NFTs) and astrocytic tangles are seen throughout the brain and tend to be more densely distributed than in Alzheimer's Disease.[68-70] Deposition of beta amyloid occurs in fewer than half the cases.[71] There tends to be a perivascular distribution with clusters around small intracortical blood vessels and a unique regional involvement of subcortical and brainstem structures.[71] Perhaps more interesting is that NFTs and even more so astrocyctic tangles tend to be found in the large white matter tracts including the corpus callosum and subcortical U-fibers along with the extreme and external capsule, and anterior and posterior commissures.[69,70] This tends to correlate with findings seen in DTI MRI studies in patients with mTBI and TBI.[51] In 2009 McKee, et al.[71] in examining the brains of one retired professional football player and two boxers found pathological changes almost identical to those described above and correlated them with memory loss, behavioral and personality changes, along with parkinsonism, speech and gait abnormalities. Since its inception Boston University's Center for the study of CTE has identified 17 cases in deceased contact sport athletes.

In addition to CTE repetitive concussions appear to be a risk for ALS. Epidemiological studies have demonstrated an

increased risk of head trauma and the development of ALS.[72] In addition, other studies have demonstrated an increased risk of ALS in Italian professional soccer players and NFL players.[73-75] McKee, et al.[76] examined 12 cases of CTE and, in 10, found a widespread TAR DNA-binding protein of approximately 43kd (TDP-43). Three of the athletes with CTE also developed signs and symptoms of progressive motor neuron disease. In these three cases, there were abundant TDP-43-positive inclusions and neurites in the spinal cord in addition to tau neurofibrillary changes, motor neuron loss, and corticospinal tract degeneration. The results suggest that TDP-43 proteinopathy seen in CTE can extend into the spinal cord and is associated with motor neuron disease.

How many concussions are too many? There are no specific guidelines on when to consider having an athlete permanently retire from contact and other sports with significant risk of concussion. When considering asking a player to retire from a sport, numerous factors need to be considered and a comprehensive analysis of the patient at least six months after the last concussive event needs to be performed. Each athlete should be considered on an individual basis, and the athlete's financial and/or social situation should never play a role in any decision. As mentioned above, a number of studies using DTI imaging in correlation with neuropsychological testing have demonstrated that in patients with positive DTI MRI studies (i.e. >2 standard deviations from normal), structural changes in the white matter likely represent permanent brain injury.[51] In addition, when looking at a subset of data from all published CTE studies there appears to be a correlation that the inheritance of an ApoE 4 allele might be a risk factor for the development of CTE.[76] Furthermore, the effects of head trauma are more severe in ApoE4-positive individuals. Therefore, any athlete with positive DTI imaging and correlative deficits on neuropsychological testing has in all likelihood suffered permanent brain injury. Other factors that should be taken into consideration include: Prolonged severe symptoms (such as greater than six months which are not responding to standard treatment), an athlete who has suffered multiple concussions over a short period of time (someone who appears to be susceptible to concussion). These individuals would be at risk for further concussion along with early onset dementia. It is recommended that these individuals permanently avoid contact and other sports with risk of concussion.

CONCLUSION

Sports related concussion continues to be the most widely publicized neurological disorder. It is becoming more evident that repeated concussion is a risk for the development of early dementia/CTE. Despite this, there is little to no evidence-based research, especially with respect to testing, management and RTP. Understanding the physiology over time at the human level is arguably the most pressing issue, as it will allow for the development of evidenced-based RTP guidelines. Evidence-based studies are also are needed to define which treatments work best for the management of the associated symptoms. Longitudinal DTI MRI studies hold significant promise as an objective measure for RTP. Despite the above, defining when a concussion has resolved remains a clinical decision. Computerized, side line and other testing are tools a neurologist can use to aid in their assessment but should never be used as the sole means to return an athlete to play. An extensive neurological history and detailed neurological exam along with the neurologist's extensive training and basic science background are still the best means to determine if and when an athlete has fully recovered from a concussion. ■

TABLE 2. STAGES OF CTE

Stage	Signs and Symptoms
1	Loss of affect and mild psychosis.
2	Social instability, erratic behavior, memory loss, and mild Parkinsonism.
3	General cognitive dysfunction progressing to dementia full-blown Parkinsonism, speech and gait abnormalities, dysarthria, dysphagia, and ocular abnormalities/ ptosis.

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