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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

SPECIAL REPORT

Take Me Out of the Ball Game: Acute Management and Long-term Consequences of Concussion in Childhood

By Matthew T. McCarthy, MD, and Barry E. Kosofsky, MD, PhD

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Dr. McCarthy and Dr. Kosofsky report no financial relationships relevant to this field of study.

SYNOPSIS: The developing brain of a child may be particularly susceptible to injury from mild traumatic brain injury, such as a concussion. Recommending a longer period of strict rest after a concussion does not provide additional benefit when compared to consensus guidelines for care after a concussion in children and adolescents. However, in retired former NFL players, exposure to tackle football prior to age 12 is associated with executive dysfunction, memory impairment, and lower estimated verbal IQ later in life.

SOURCES: Thomas DG, et al. Benefits of strict rest after acute concussion: A randomized controlled trial. *Pediatrics* 2015;135:213-223. Stamm JM, et al. Age of first exposure to football and later-life cognitive impairment in former NFL players. *Neurology* 2015 Jan 28. pii: 10.1212/WNL.0000000000001358. [Epub ahead of print]. Filley CM, Bernick C. Children and football: A cautionary tale. *Neurology* 2015 Jan 28. pii: 10.1212/WNL.0000000000001357. [Epub ahead of print].

There has been increasing awareness of the incidence and potential long-term consequences of mild traumatic brain injury (mTBI) in children and young adults. While parents, school systems, and athletic programs are clamoring for evidence-based guidelines, the field remains primitive in our understanding of the factors, resulting in a spectrum of individual outcomes. Most individuals who sustain mTBI make complete recoveries, 80% within the first month, though some with ongoing symptoms exhibit sustained neurocognitive deficits. While numerous

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consensus "return to school and play" guidelines have been created in recent years, they are limited by the relative lack of data regarding the acute management and potential long-term outcomes after a concussion. This lack of evidence is most apparent in relation to pediatric concussion. These two studies serve to fill that knowledge gap by evaluating the potential impact of concussions on developing brains — one looking at the recommendations for management immediately post-injury and the other investigating long-term cognitive outcomes related to this type of head injury in childhood.

In the first study from Thomas et al, the authors conducted a randomized, controlled trial assessing specific recommendations for strict rest following a concussion. Eighty-eight patients aged 11-22 years presenting to a pediatric emergency department within 24 hours of a concussion were randomized to receive instructions for either the standard of care (1-2 days of rest, followed by a stepwise return to normal activity once symptoms had resolved) or 5 days of strict rest. Each participant completed a symptom rating scale, neurocognitive testing, and balance assessment at initial presentation, and then 3 and 10 days later. Activity level was self-reported by participants using diaries to account for their level of activity throughout each day.

By randomly assigning participants to either be instructed to adhere to the standard of care or strict rest for 5 days, the authors showed the following:

1) Both groups showed about 20% decrease in energy expenditure and physical activity over the first 5 days post-injury.
2) The strict rest group reported fewer hours of moderate and high mental activity in days 2-5 post-injury.
3) There were no significant differences between groups in neurocognitive testing and balance scores at day 3 and day 10.
4) Individuals in the strict rest group took longer to report symptom resolution, had overall higher symptom scores over the 10-day study period, and had higher mean symptom scores on a daily basis. This was especially apparent with physical and emotional symptoms.
5) Individuals with a past history of concussion reported more symptoms at day 10 in the strict rest group compared to the standard-of-care group, while individuals with a first-time concussion showed no difference between groups.

In the second paper by Stamm et al, the authors divided a group of former NFL players between the ages 40-69 years based on the age at which they were first exposed to tackle football (< 12 years or ≥ 12 years). The players were selected from a group comprised of individuals with recent cognitive, behavioral, or mood complaints. Each participant performed a series of standardized cognitive evaluations that measured executive function, memory, and estimated verbal IQ. After controlling for level of education, total duration of football play, and multidimensional correlation between tests and within subjects, the age of first tackle football < 12 years group performed significantly worse than the age of first tackle football ≥ 12 years group on every measurement. The total number of concussions reported was not significantly different between the two groups.

■ COMMENTARY

These studies focus on the acute management and potential long-term consequences of concussion in children and adolescents. Previous studies have led to disparate conclusions: Some have reported that children are able to make quicker and more complete recovery from a concussion due to greater neuronal plasticity. Others have concluded that concussion is one of the few injuries from which children recover more slowly than adults, and that they may be more susceptible to long-lasting consequences from this type of injury resulting from important developmental processes that may be disrupted by an injury during this critical period of brain maturation.

The first study begins to fill an important gap regarding specific recommendations for return to activity after a concussion in pediatric patients. It represents one of the first randomized, controlled trials evaluating such specific recommendations. Despite the numerous consensus, evidence-based guidelines that have been published

recently, there have been relatively few specific recommendations for children that are based on class I evidence. For the most part, these guidelines extrapolate from adult literature and use consensus expert opinion to suggest using a more conservative approach in children given the relative lack of studies available. With this study, the authors were able to test one specific element of return to activity recommendations and demonstrated that the standard of care recommendation after an acute concussion (1-2 days of rest followed by gradual step-wise return to activity after symptoms have subsided) is preferred to an approach using a longer, strict rest period.

One possible limitation in this study is that while the strict rest group did comply with reducing mental activity compared to the standard-of-care group, they may not have adhered to strict physical rest. Additionally, there is a chance that the higher symptom scores in the strict rest group may have been the result of reporting bias. In particular, the discharge instructions may have had an influence on the perceived seriousness of the injury, leading to a change in symptom reporting, rather than actually leading to a difference in recovery between the two groups. In addition, these results may not be generalizable to all children with concussions, as this study only recruited patients who presented to the emergency department within 24 hours of an acute concussion and were discharged home. This does not take into account patients who present with persistent symptoms days after an injury or patients with more severe injuries requiring hospitalization, two groups who may benefit from an extended period of strict rest. With these caveats in mind, this report provides much needed data to help clinicians provide appropriate, evidence-based advice to their patients and families.

In the second study, the authors make an important contribution to help establish a link between concussions suffered by young children and subsequent long-term cognitive dysfunction. It has been assumed for some time that repetitive head injuries in childhood and adolescence likely impact brain development and can have long-term consequences on cognitive function. This study establishes that the risk might be even higher for permanent sequelae if the head injuries occur at a younger age during periods of critical brain development. However, it is not known what fraction of football players sustain such ongoing symptoms. These results may not be generalizable to all populations, as the study participants were all former professional football players who are currently reporting cognitive, mood, or behavior problems. There is a much larger population of people who only play tackle football as children and adolescents who would be of interest for a similar investigation. Additionally, there may be baseline differences in verbal and cognitive abilities between children drawn to playing tackle football at an earlier age and those who do not play until they are older, as well as between individuals who do and don't choose to play professional football. Importantly, the authors are very clear to state that although executive dysfunction and memory problems are common features of chronic traumatic encephalopathy (CTE), the results of this study do not suggest that any of the study participants have or will develop CTE. While it is conceivable that repetitive head injuries eventually lead to the pathologic changes seen in CTE, the relationship between the two is still not established and CTE remains exclusively a neuropathologic entity.

The developing brain may be uniquely susceptible to concussion, with lasting consequences on brain structure and function. However, most pediatric patients demonstrate complete recovery within days to weeks of concussion. This paradox places clinicians in a difficult situation when counseling parents and caring for children who have sustained concussions, particularly student athletes focused on rapidly returning to play. Recent guidelines published by leading thinkers and professional societies have established recommendations advising a stepwise, graded return to school and play. Those consensus statements acknowledge the need for additional research to improve the diagnosis, inform the prognosis, and facilitate the recovery of those children at risk for ongoing symptoms following concussion. These two studies are both significant in that they specifically studied pediatric populations to help develop strategies for prevention and management of concussions in this population. The results of these two studies are, in fact, coherent: Clinicians should recommend delaying the initial age of tackle football to ≥ 12 years, and following a concussion in individuals ≥ 11 years should recommend a stepwise return to normal activity once symptoms have resolved. As more data become available from studies in children, neurologists will be able to make better evidence-based recommendations for appropriate management. These studies are an essential step in that direction, and are much needed, as increasing participation in youth sports makes children the largest group of individuals at risk for concussion. ■

ABSTRACT & COMMENTARY

Neuroimaging Differences in Dyslexics: Chicken or Egg?

By Alon Seifan, MD, MS

Assistant Professor of Neurology, Weill Cornell Medical College, Memory Disorders Program

Dr. Seifan reports no financial relationships relevant to this field of study.

SYNOPSIS: Neuroanatomical differences in primary sensory cortices may distinguish dyslexic individuals from non-dyslexic individuals, providing a potential biomarker for identifying adults who may be predisposed to developing atypical neurodegenerative disease.

SOURCE: Clark KA, et al. Neuroanatomical precursors of dyslexia identified from pre-reading through to age 11. *Brain* 2014;137: 3136-3141.

Developmental dyslexia is a reading disorder characterized by difficulty in learning to decode print. According to the revised *Diagnostics and Statistics Manual – V* criteria for specific learning disabilities (SLD), dyslexia is one of three specific learning disabilities. SLDs can manifest as impairment of reading, writing, or math. Individuals with dyslexia, now called "SLD with impairment in reading," have reading difficulties that persist despite targeted instruction, with skills substantially below those expected for age, causing functional disability. Onset is almost always during the school-age years. For a diagnosis of SLD, concomitant intellectual disabilities and attention deficit hyperactivity disorder (ADHD) should not be present.

The prevalence of dyslexia is estimated at 7%. Dyslexia is a constitutional condition, implying a predisposition beginning at birth. Reading requires higher-level cognitive processes such as integration of basic sensory information, as well as lower-level processes such as those related to basic sensory input. Most individuals with dyslexia display difficulty with phonological awareness, rapid naming, and verbal working memory, all of which are necessary for reading ability. Structural and functional imaging studies across alphabetic languages consistently reveal alterations in gray matter and white matter in affected individuals, specifically within the left posterior language system. However, despite decades of research, it remains unclear which brain differences represent the cause of behavioral difficulties in dyslexia and which result from reduced reading experience. To answer these types of questions, longitudinal studies of preliterate children are required.

The recent study by Clark et al specifically uses a longitudinal approach to identify brain differences that could predate literacy acquisition. The goal was to quantify how cortical thickness evolved over time, with the first magnetic resonance imaging (MRI) measurement taken at age 6, which is 1 year prior to the age that children learn to read. The study initially recruited 52 children to be followed longitudinally with neurocognitive and structural MRI measurements taken from preschool to age 11 years; 39 of these children participated in the study. Subjects with high and low risk for dyslexia were chosen from a cohort of Norwegian children who were part of the Bergen Longitudinal Dyslexia Study. Individuals with mental retardation, ADHD, or other neurological impairment (including vision or hearing impairment) were excluded. Dyslexia was defined as scoring below the 25th percentile in two or more literacy tests. Using this definition, 11 subjects were ultimately diagnosed with dyslexia.

At the first MRI at age 6 years, children who were later diagnosed with dyslexia, as compared to those who were not, showed significantly thinner cortex in five regions of interest, some of which subserve primary sensory processes and others higher-level associative processes. Specifically, thinner cortex was observed in primary auditory and visual cortex (Heschl's and lingual gyri, respectively), and in heteromodal cortex (middle cingulate, medial frontal, and orbitofrontal gyri). By the time the children had learned to read, cortical thickness differences were no longer apparent in any of the regions except Heschl's gyrus, which remained significantly thinner in dyslexics vs controls. This implies the presence of reduced neuroanatomical capacity to process auditory information in children destined for dyslexia and does not fully normalize with reading acquisition. The study suggests that atypical development of primary sensory cortex, particularly within Heschl's gyrus, is fundamental to the reading deficits and related cortical differences observed in some dyslexics.

■ COMMENTARY

Despite almost 100 years of research into dyslexia, consensus regarding the underlying pathology has

been difficult to achieve. Studies have often conflicted regarding specific location of abnormality, probably because the dyslexia reality represents a heterogeneous group of related disorders. For example, there appear to be at least two subgroups, one with primarily sublexical impairment (poor non-word reading) and another subgroup with primarily lexical impairment (poor irregular word reading); mixed lexical and sublexical subtypes also exist. Complicating matters further, reading disabilities are often comorbid with math disabilities, ADHD, and other language disorders. The study by Clark et al did well to exclude individuals with ADHD and intellectual disabilities, but did not take into account comorbidity with other SLDs such as dyscalculia. Thus, the extent to which the findings are specific to SLD with reading impairment remains unknown.

Another common challenge regarding neuroimaging studies of dyslexia, and particularly with meta-analyses, is the fact that individuals with similar ages can often be at quite different developmental stages. Major developmental changes are occurring even on a year-to-year basis in children, so studies (in particular, meta-analyses) that combine children into age groups may miss important developmental changes. The study by Clark et al avoids this problem by imaging the children at specific ages, but the presence of individual-level variation in developmental trajectories could still confound the findings. Another important thing to note is the fact that although children had not learned to read independently until age 7 years, the initial MRI measurements at age 6 may reflect neuroanatomical changes from pre-literacy training, including years of exposure to print and reading. Longitudinal imaging studies of dyslexia can help us to understand which brain differences cause dyslexia and which result from impaired reading experience. ■

ABSTRACT & COMMENTARY

How Common Are Neuromuscular Disorders?

By Michael Rubin, MD

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Dr. Rubin reports no financial relationships relevant to this field of study.

SYNOPSIS: Although many specific neuromuscular disorders are rare, in aggregate, these all add up to a large number, roughly twice as common as multiple sclerosis, and about the same prevalence as Parkinson's disease.

SOURCE: Deenen JCW, et al. The epidemiology of neuromuscular disorders: A comprehensive overview of the literature. *J Neuromusc Dis* 2015; DOI 10.3233/JND-140045.

Studies on population frequencies of inherited neuromuscular diseases around the world were first published in 1991,[1,2] with additional reports surfacing in 2010 from the Muscular Dystrophy Campaign, and in 2013 from the Orphanet Report Series, the latter of which included rare neuromuscular disorders. Given improved diagnostic capabilities with the advent of molecular genetics, and consensus on diagnostic criteria, an up-to-date review of the scientific literature since 1990 was undertaken to determine occurrence rates, and gender and age distributions of various neuromuscular disorders.

Using keywords "epidemiology," "incidence," and "prevalence," and searching for original English language articles whose titles included the terms neuromuscular or neurological disorder, and neuromuscular or muscle disease, PubMed was searched for peer-reviewed articles appearing between January 1990 and July 2014, covering 30 relatively frequent or phenotypically distinguishable neuromuscular diseases. Arranged anatomically, these conditions included anterior horn cell disorders, such as progressive spinal muscular atrophy and amyotrophic lateral sclerosis, and peripheral nerve disorders, such as Charcot-Marie-Tooth disease, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre' syndrome, and chronic idiopathic axonal polyneuropathy. Myasthenia gravis and Lambert-Eaton myasthenic syndrome were the neuromuscular junctionopathies included, while muscle diseases studied included the entire gamut of muscular dystrophies, inflammatory myositides, chronic progressive external ophthalmoplegia, and Pompe's and McArdle's disease. Secondary disorders, such as diabetic or HIV neuropathies, were excluded, and where multiple publications incorporated the same data, only the most recent data were included.

Among 169 relevant articles identified, incidence rates were identified for 11 disorders, ranging from 0.05/100,000 for Lambert-Eaton myasthenic

syndrome to 9/100,000 for spinal muscular atrophy. Prevalence rates were identified for 24 disorders, ranging from 0.1/100,000 for oculopharyngeal muscular dystrophy to 60/100,000 for post-polio syndrome. Prevalence rates lower than 50/100,000 were found in 23 diseases, making them rare by definition, but summating the prevalence rates for the 24 disorders so obtained brought the total to 160/100,000. Age distribution was ambiguous in five disorders, but occurred early in life in Friedreich ataxia and in Duchenne and congenital muscular dystrophies, and later in life in amyotrophic lateral sclerosis, post-polio syndrome, and Lambert-Eaton myasthenic syndrome. Overall, disorders were equally distributed between the sexes for the 18 disorders in which it was available, but men featured more prominently in amyotrophic lateral sclerosis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, Lambert-Eaton myasthenic syndrome, and Duchenne, Becker, and facioscapulohumeral dystrophy, whereas women were twice as affected in myasthenia gravis, non-dystrophic myotonia, polymyositis, and dermatomyositis. No information was available for Pompe's or McArdle's disease, chronic idiopathic axonal polyneuropathy, idiopathic neuralgic amyotrophy, or progressive spinal muscular atrophy. Although individually rare, as a group neuromuscular diseases are not, being twice as high as multiple sclerosis (80/100,000 in Europe) and similar to that seen with Parkinson's disease (100-300/100,000 worldwide). Since 1990, considerably increased prevalence rates seem to have occurred in Charcot-Marie-Tooth disease, and in Becker, facioscapulohumeral, and myotonic muscular dystrophy, with the latter prevalence appearing twice as high compared to 1991. Genetic testing may be a significant contributing factor.

■ COMMENTARY

To determine the incidence and prevalence of inflammatory myopathies, original articles in English or French were reviewed, of which 46 were found, published between 1966-2013, wherein prevalence or incidence were discussed.[3] Prevalence ranged from 2.4-33.8 per 100 000, and incidence from 1.16-19 per million/year, with no clear geographical disparities found. In the northern hemisphere, possibly due to ultraviolet radiation and its immunomodulatory effects, the incidence of dermatomyositis followed a latitudinal gradient, whereas sporadic inclusion body myositis prevalence correlated with HLA-DR3 frequency. Inflammatory myopathies are rare and may be influenced by genetic and environmental factors. ■

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ABSTRACT & COMMENTARY

Predictors of Refractory Status Epilepticus

By Padmaja Kandula, MD

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Dr. Kandula reports no financial relationships relevant to this field of study.

SYNOPSIS: In a combined derivation and validation study, three independent risk factors for refractory status epilepticus were identified — acute symptomatic cause for seizures, stupor or coma, and a low serum albumin < 35 g/L.

SOURCE: Sutter R, et al; Early predictors of refractory status epilepticus: An international two-center study. *Eur J Neurol* 2015;22:79-85.

Over the years, the consensus definition of refractory status epilepticus has evolved into the persistence of the ictal state after failure of first- and second-line antiepileptic agents. However, the aggressiveness of treatment is still under fierce debate. The potential risk-to-benefit ratio of anesthetic treatment, along with limited technical resources at many hospitals, continues to plague practitioners. In this study, Sutter et al tried to predict refractory status epilepticus by applying available clinical information to a matched European derivation data set and a U.S. validation set.

The authors identified 171 patients from the Swiss derivation data set and 131 patients from a U.S. validation set from 2005-2012 after exclusion of post-anoxic status epilepticus. Status epilepticus was defined as clinical and electroencephalographic seizure activity lasting at least 5 minutes or seizures without interval recovery. Etiology (acute vs non-acute), level of consciousness (awake/somnolent vs stuporous/comatose), and serum albumin levels were recorded in all patients. All included patients underwent continuous electroencephalography (cEEG) or samples of > 20 minutes of EEG every 12

hours, where continuous EEG was not available. A uniform treatment protocol with initial benzodiazepine treatment followed by intravenous phenytoin/fosphenytoin, valproic acid, levetiracetam, or combination thereof was standardized for all patients. After failure of the above first- and second-line agents, anesthetic coma was subsequently induced. The primary outcome (refractory status) was defined as clinical and/or electrographic status persistence despite first- and second-line therapy.

The percentage of patients with refractory status epilepticus was 45% in the derivation set and 46.6% in the validation set. Acute status epilepticus etiology, coma/stupor, and serum albumin < 35 g/L at status onset were independent predictors for refractory status in the derivation data set (odds ratios = 2.02, 4.83, and 2.45, respectively, for the three clinical conditions). These results were externally validated with an independent U.S. validation set.

■ COMMENTARY

Although retrospective in nature, this study by Sutter and colleagues identified three useful, readily available clinical parameters to assess potential refractory status epilepticus. The use of two large cohorts also allows a good prediction and validation model. On the other hand, the relatively younger average age (66-67 years) of both cohorts and exclusion of post-anoxic status epilepticus limits generalization of these results. In addition, cases in which only periodic routine EEG was available may have missed subclinical or electrographic status with a subsequent bias toward a more favorable outcome. A further prospective trial with larger sample size to allow adequate status etiology sub-typing (including anoxic status) has the potential to be useful in prognostication and allocation of resources influencing aggressiveness of overall treatment. ■

Neurology [ALERT®]

Stroke Alert

By Matthew E. Fink, MD

Report from the International Stroke Conference 2015

Major announcements at the International Stroke Conference 2015 in Nashville, Tennessee, included reports on three trials that compared endovascular clot retrieval for acute ischemic stroke, compared to medical treatment with intravenous thrombolytics alone. In a stunning reversal of the negative studies that were reported just 1 year ago, three trials all reported positive results. In the EXTEND–IA trial, more brain was reperfused 24 hours after endovascular thrombectomy in patients who also received intravenous alteplase, than those getting IV thrombolytic treatment alone. In the SOLITAIRE-F stent-retriever device study, where the intra-arterial device was deployed within 4.5 hours of stroke onset, functional independence at 90 days, based on the modified Rankin score, was better than treatment with IV thrombolytics alone. The third trial, ESCAPE, was a similar comparison between usual medical care, usually intravenous alteplase, compared to available embolectomy devices within 12 hours of onset, and even with such a delay, there was a significant downward shift in the modified Rankin score with the intervention group showing better functional outcome at 90 days, 53% vs 29% in the modified Rankin score 0-2. The ESCAPE trial also showed a reduction in 90-day mortality, in favor of the interventional treatment, 10.4% vs 19%.

Why did these studies show improved outcome when similar trials in the past have failed? These new devices were improved technologically, the interval from onset of symptoms to puncture and endovascular treatment was generally shorter, and patient selection was excellent with the use of CT angiography to identify large vessel occlusions in a rapid fashion.

The studies are being simultaneously published in the *New England Journal of Medicine*, and more details will be available for all of us to review. These recent reports will usher in a new era in acute ischemic stroke therapy. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

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CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

CME QUESTIONS

1. Which of the following statements regarding concussion in children is false?
a. Most children with mild traumatic brain injury make complete recoveries.
b. A brief period of rest, followed by stepwise return to activity, results in the best outcomes.
c. There are no clear biomarkers that predict long-term symptoms in children who sustain a concussion.
d. Early play of tackle football (before age 12) may result in long-term sequelae.
e. Children are the largest group at risk for traumatic brain injury.

2. Dyslexia is characterized by the following?
a. Dyslexia is a psychological disorder treatable with psychotherapy.
b. Dyslexia is a form of learning disability that is correlated with changes in brain morphology.
c. Dyslexia remains constant throughout life.
d. Dyslexia occurs only in boys.

3. Neuromuscular diseases as a group occur with a frequency similar to that seen with which of the following?
a. Parkinson's disease
b. Multiple sclerosis
c. Epilepsy
d. Stroke
e. Headaches

4. Refractory status epilepticus is a state of critical illness that is defined as which of the following?
a. Epileptic seizure that does not respond to initial intravenous therapy.
b. Epileptic seizures that are continuous for > 1 hour.
c. Epileptic seizures that fail to respond to first- and second-line therapies.
d. Epileptic seizures that result in death.

[IN FUTURE ISSUES]

Update on Movement Disorders