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Short Takes

Steven G. Pavlakis, MD *

The Brooklyn Hospital, Department of Pediatrics and Icahn School of Medicine at Mount Sinai, Brooklyn, New York

White matter integrity and processing speed in sickle cell anemia. *Neurology* 2018;90:e2042-e2050. Doi:10.11212/WNL.0000000000005644

Stotesbury H, Kirkham FJ. Kolbel M, et al.

Flash Summary: The authors studied white matter integrity in sickle cell anemia (SCA) and correlated white matter changes to reduced processing speed index (PSI). Between 2015 and 2016, the study recruited and evaluated 83 SCA patients. Each patient underwent T2-Weighted MRI and diffusion weighted sequences. The images were processed to calculate tract-based measures of white matter integrity, including diffusion tensor imaging and neurite orientation dispersion as well as density imaging parameters.

The primary outcome was PSI and this was compared to siblings. Patients with SCA had a lower mean PSI. Among the patients, 45% had silent cerebral infarctions (SCI); however patients with or without SCI did not differ in mean PSI. In patients with lower PSI, lower values were associated with reduced fractional anisotropy, reduced intracellular volume fractions, and increased mean diffusivity and increased radial diffusivity.

Bottom Line: There is one main question left in SCA. We know that stroke and even SCI are correlated to cognitive disability in the population. However, we do not know why patients with SCA develop cognitive disabilities in the absence of stroke and SCI.

Many believed that the relative hypoxemia and perfusion insufficiency result in cognitive deterioration over time even without an MRI correlate of stroke or SCI. The pathophysiology of this cognitive deterioration is most likely related to white matter damage since the white matter represents the border-zone in SCA. Here, the authors confirm this hypothesis. Since stroke in SCA is essentially solved with transcranial Doppler monitoring. The remaining question is how do we prevent the white matter deterioration in SCA? Possible targets that need to be studied include nocturnal hypoxemia, relative anemia, and relative hypertension. The cognitive deterioration found in SCA without overt or subclinical stroke is the last frontier in regard to intervention, until SCA is cured with genetic interventions.

Eteplirsen treatment for Duchenne muscular dystrophy. Exon skipping and dystrophin production. *Neurology* 2018;90: e2146-e2154. doi:10.1212/WNL.000000000005680

Charleston JS, Scnell FJ, Dworzak J et al.

Flash Summary: This study aims to answer the question about whether eteplirsen induces novel dystrophin expression in patients with Duchenne muscular dystrophy (DMD).

This study examined 12 boys with DMD due to exon 51-skipping. These boys completed an earlier trial for eteplirsen treatment and were on corticosteroids with stable disease. All could walk 180 to 440 meters on a six-minute walk test. This was an open label observational study. Patients were treated with weekly IV eteplirsen. Deltoid muscle biopsies were taken after week 180. The primary outcome was dystrophin expression on muscle biopsy samples.

Compared with untreated muscle samples, biopsies from eteplirsen-treated patients had greater dystrophin expression.

Bottom Line: This study shows that treated patients had increased dystrophin expression compared with untreated patients. In an accompanying editorial, etiplirsen is described as a novel antisense oligonucleotide that results in skipping of exon 51, restoring the reading frame and generating a truncated dystrophin. Eteplirsen was approved in 2016 for patients with exon 51-exon skipping. The editorial opines that the FDA approval was controversial with questions about sample size and the degree of increase in dystrophin.

Here, muscles treated with eteplersen clearly showed increases in dystrophin. All treated patients had below a 4 % dystrophin level. In Becker muscular dystrophy, dystrophin levels are about 40% of normal, resulting in a milder phenotype compared to DMD. The editorial opines that the increase in dystrophin levels occurring from eteplirsen may not be meaningful clinically.

I'm not certain that this article makes the use of eteplirsen compelling as a clinical treatment of DMD. Indeed, it made me question the clinical effectiveness of the treatment even more than before. In fact, in retrospect it makes the approval of eteplirsen more tenuous.

A better study would have been a correlation of dystrophin percent to clinical measures. Here, all we have is a drug that

Editor's note: Short Takes offers a brief analysis by Steven G. Pavlakis of selected articles that may be of interest to child neurologists. Papers that strike the fancy of the analyst or the editors are selected for inclusion, but we welcome suggestions.

* Communications should be addressed to: Steven G. Pavlakis; The Brooklyn Hospital; Department of Pediatrics and Icahn School of Medicine at Mount Sinai; 121 DeKalb Ave; Brooklyn, NY 11201.

E-mail address: SPavlakis@maimonidesmed.org

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increases dystrophin but no clear indication of clinical effectiveness of increased dystrophin at these levels.

This is a drug company-funded study with the first and corresponding author having a company email, namely a Sarepta email. Second, this study is limited even though it has a positive outcome.

This is a potentially exciting treatment based on a real genetic understanding of about 14 % of DMD children. The treatment effectiveness seems controversial. This is a small study that really shows us no clinical information and only buttresses the Sarepta approach to DMD treatment, a treatment that is already approved. Much more needs to be done, even though this drug has been approved. This study adds very little to our understanding of treatment effect.

Age of first exposure to tackle football and chronic traumatic encephalopathy. *Ann Neurol* 2018;83:886-901
Alosco ML, Mez J, Tripodis, Y et al.

Flash Summary: This study aimed to examine the effect of age of first exposure to tackle football on chronic traumatic encephalopathy (CTE) pathological severity. The study also aimed to determine age of first exposure with age of neurobehavioral symptom onset. The study included 246 tackle football players who donated their brains. Two hundred eleven were diagnosed with CTE and 35 were without CTE. Informant interviews assessed age of onset of neurobehavioral symptoms. Results showed that age of tackle football exposure was not associated with CTE neuropathological severity. In the 211 participants with CTE, every one-year younger participants played tackle football predicted earlier reported cognitive symptom onset by 2.4 years and behavioral mood symptoms by 2.5 years. Age of tackle footbal l participation before 12 years predicted cognitive and mood symptoms by about 13 years earlier. The authors conclude that younger age of exposure to tackle football was not associated with CTE pathology severity but predicted earlier neurobehavioral symptom onset.

Flash Summary: This research is limited by the ability to recruit samples and obtain clinical data. It is difficult to obtain clinical data from a postmortem pathological sample. Here, the authors performed interviews of family members and age of first symptoms was entirely by recollection. This is a real bias that cannot be overcome. Furthermore there was no association between age at onset of playing tackle football and severity of CTE neuropathology.

The main finding was the very strong association of playing tackle football and age of onset of both cognitive and neurobehavioral symptoms. If tackle football started before age 12, onset of symptoms occurred 13 years earlier.

Here, we have data suggesting that early tackle football exposure may result in clinical cognitive and neurobehavioral symptoms. Although recall bias is the main fault in this data, it is a study suggesting that early exposure to tackle football may result in early cognitive and behavioral disabilities. Certainly more data is necessary to confirm these findings. It should be understood that more data may be hard to come by unless we fund a prospective study of all young players who participate in contact sports with decades-long follow-up. This might be the only way to confirm this study's findings.

I think child neurologists need to start chiming in to the dangers of early contact sports. It is in our purview as neurologists; we need to be at the table with government agencies, schools and parent groups to remain relevant as pediatric neurologists in improving the health of children.