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***APOE* ϵ 4 Status and Traumatic Brain Injury on the Gridiron or the Battlefield**

Sam Gandy* and

Mount Sinai Chair in Alzheimer's Disease Research, Director of the Center for Cognitive Health and the NFL Neurological Program, Associate Director of the Alzheimer's Disease Research Center, and Professor of Neurology and Psychiatry, Mount Sinai School of Medicine and the James J. Peters VA Medical Center, New York, NY 10029, USA.

Steven T. DeKosky*

Vice President and Dean, James Carroll Flippin Professor of Medical Science and Professor of Neurology, University of Virginia School of Medicine, Charlottesville, VA 22908, USA.

A FEW WEEKS AGO, FORMER SAN DIEGO CHARGER JUNIOR SEAU DIED OF AN Apparently self-inflicted gunshot wound to the chest. This news immediately brought to mind a similar suicide in February 2011—that of former Chicago Bears football player Dave Duerson, who left a note indicating that he had chosen a method of suicide that preserved his brain so it could be examined for signs of chronic traumatic encephalopathy (CTE). In CTE, the brain contains deposits consisting of neurofibrillary tangles of aberrantly phosphorylated tau protein similar to those found in the brains of Alzheimer's disease (AD) patients, and appears identical to the pathology found in boxers, previously known as dementia pugilistica. As of this writing, we don't yet know whether Seau's brain shows CTE, but there is accumulating evidence that traumatic brain injury (TBI) from repeated concussions and subconcussive injuries suffered in high-impact sports such as American football, ice hockey, and professional wrestling can lead to CTE; the dementia is clinically somewhat similar to AD (1, 2). In 2010, a recent college graduate and collegiate football player committed suicide and proved to have CTE at autopsy. His was the youngest documented case of CTE, providing highly suggestive evidence that certain children and adolescents are at risk for developing CTE because of their exposure to high-impact sports. CTE has also been identified in military veterans of the Iraq and Afghanistan Wars, apparently a result of their repeated exposure to blast injuries from improvised explosive devices (IEDs) (2, 3).

Some of the blame for dementia can also be placed on genetics. Carriers of one or two copies of a particular allele for apolipoprotein E (*APOE*) are more likely to get AD. Carrying a single *APOE* ϵ 4 allele increases a person's relative risk for developing AD late in life by threefold. Two *APOE* ϵ 4 alleles increase the relative risk for AD more than 10-fold. In fact, 50% of late-onset AD patients have at least one *APOE* ϵ 4 allele. On the basis of our

*Corresponding authors. samuel.gandy@mssm.edu (S.G); dekosky@virginia.edu (S.T.D.).

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own experience studying the CTE-like pathology arising from TBI in boxers with dementia (4), we predict that the risk for neurological disability from sports-associated and blast-associated CTE is also increased by the presence of one or two alleles of *APOE* ϵ 4. Indeed, when a person who is heterozygous for the *APOE* ϵ 4 allele suffers TBI, the effect on his or her relative risk for dementia is synergistic and increases by 10-fold or more (5).

The idea that potentially avoidable repetitive TBI could contribute to the eventual development of dementia is an unsettling thought for physicians—and for some in the media. A recent public debate (“Ban College Football!” Intelligence² debates) and an article in a January *New Yorker* (“Does Football Have a Future?”) speculate about the eventual demise of football, in part because of TBI risks. Nonetheless, there has been little discussion about possible public health benefits of *APOE* genotyping of high school athletes who intend to participate in impact sports or of prospective military personnel. Is *APOE* genotyping feasible, and could it help to avert dementia in susceptible persons exposed to TBI through sports or battlefield service?

To help address this question, we performed an informal e-mail poll of experts in AD, TBI, and CTE to estimate their attitudes and practices. Forty-five (95%) responded, voting 2:1 against using our current knowledge of *APOE* genotyping to guide decisions about adolescent participation in high school or college sports. Interestingly, the response was an even stronger 3:1 “nay” vote when it came to the idea of genotyping prospective armed services enlistees. None of the experts polled had ever used this information in their own lives. However, nearly half said that they would use *APOE* genotyping in making sports play decisions for their own children if there had been incidental documentation of *APOE* ϵ 4 alleles in the family (for example, if a grandparent with AD was known to be an *APOE* ϵ 4 carrier). We noted with interest this dissonance between willingness to use *APOE* genotype information that was determined for other reasons but reluctance toward *APOE* genotyping explicitly for making a sports/military exposure decision.

The consensus was clear: Most of the experts we consulted believe that it is premature to introduce *APOE* genotyping into schools or the military now. They generally feel that we need much better data on which to base a decision. But what type of information would allow us to properly evaluate the utility of *APOE* ϵ 4 status for decisions about exposing children, adolescents, or adults to the risks of TBI in sports or in the military?

We know that *APOE* ϵ 4 alleles are overrepresented among boxers coming to medical attention because of clinical evidence of CTE (4). However, we lack several key pieces of quantitative information upon which to base recommendations to young athletes or military personnel. First, since there is no systematic registry, screening, or genotyping of at-risk individuals, we cannot estimate the prevalence of CTE, the proportion of CTE patients who have *APOE* ϵ 4 alleles, or the relative risk of sports or military exposure to carriers and noncarriers of *APOE* ϵ 4 alleles. Most existing data on *APOE* ϵ 4 and dementia risks are from cross-sectional studies of mid- to late-life AD cohorts and age-equivalent healthy controls, and so these results cannot be assumed to apply to the subjects at risk for CTE, whose exposure may begin during adolescence. Also, for CTE, we do not know the natural course of the disease. The variable but usually long latency between initial exposure to TBI and the

appearance of clinical dementia is a major challenge in establishing the etiologies of CTE. Second, we have no prospective, population-based natural history data that would reveal whether *APOE* genotyping at an early age can predict the eventual development of CTE in TBI-exposed people. Such studies would need to assess subject ethnicity because *APOE* ϵ 4-mediated relative risk for AD in African Americans and Hispanics may be somewhat attenuated, and this probably applies to CTE as well.

One approach to collecting the necessary data would be to set up a network of TBI/CTE Research Centers modeled on the national network of AD Research Centers with brain banks, clinical, neuropathological, educational, and data programs, as well as basic and clinical research projects. This would enable a critical experiment: A cohort of subjects would be recruited, including high-risk adolescents exposed to sports-related TBI and representing all three *APOE* genotypes (ϵ 2, ϵ 3, and ϵ 4). Various ethnicities would be represented across all *APOE* genotypes because, as mentioned above, African and Hispanic heritage can modify the relative risk of *APOE* ϵ 4 alleles. Subjects would maintain lifelong concussion diaries, and, to the extent available, they would wear electronic monitoring “smart helmets” to estimate the forces, vectors, and torque acting upon their brains. These measures, taking into account genetic susceptibility together with the nature, severity, and number of TBIs, and in the context of surveillance for clinical and biomarker evidence for neurodegeneration that might herald CTE, could form the basis for predictive mathematical models that could then be tested for their reliability in identifying those at highest risk for CTE. The length of the latency period between TBI and onset of CTE is measured in decades, so the acquisition of these data will constitute a large, long, and expensive effort. If *APOE* ϵ 4 allele carrier athletes are found to be more susceptible to CTE after a typical course of sports-inflicted TBI, we will want to seriously consider *APOE* genotyping of prospective soldiers or athletes. Knowledge of their child’s *APOE* genotype may change parents’ decisions whether to sign the informed consent and release required for their children to play high-impact sports.

There are several cohorts already being assembled that might provide some relevant prospective longitudinal data on TBI. For example, the proposed National Institute of Child Health and Development Vanguard Study will document the major life events and environmental exposures of 100,000 children until their 21st birthdays. Chronicling the head and sports injuries of these children would yield valuable prospective, longitudinal data. Also of interest would be evaluation and follow-up of members of the National Football League Hall of Fame or prospective studies of professional football players. TBI-related questions are already being integrated into the U.S. Department of Defense-Alzheimer’s Disease Neuro-imaging Initiative. Under this new initiative, military personnel and veterans at high risk for exposure to IEDs will provide DNA for genetic research (including *APOE* genotyping) and will undergo serial assessments of cognitive status, brain structure, and a panel of imaging and body fluid biomarkers.

Ethical and psychological issues complicate any solution to this problem. There is the very real concern about the effect of genotype information on family members and on personal employability and insurability. Although the federal Genetic Information Nondisclosure Act (GINA) and state-level efforts were established to shield patients from discrimination

according to genetic information, GINA has not been tested in court. In practice, GINA only protects patients if genotype information is kept separate from the main medical record, which may not happen routinely. In addition, recruiting high school-age subjects for *APOE* genotyping and follow-up could be controversial as parental informed consent would be required, necessitating pretest genetic counseling for adolescents and their parents. Although *APOE* genotypes would not be disclosed during the study, the purpose of the research would need to be explained carefully during the informed consent process. In the event that unintentional disclosures were to occur, this counseling would provide families with a firm basis for understanding the potential consequences.

In spite of the obstacles to considering *APOE* genotyping for high schools and the military, it is—without doubt—a worthwhile challenge. In the United States alone, there are an estimated 1.1 million high school football players. The prevalence of *APOE* ε4 homozygosity and heterozygosity (in Caucasian populations) are 2 and 20%, respectively. Therefore, the *APOE* genotyping issues discussed here apply to somewhere between 22,000 and 220,000 athletes. The RAND Corporation estimates the total number of Iraq and Afghanistan veterans with TBI diagnoses at 285,000. Adding to the emotional cost to the patient and family of years of slow cognitive decline, culminating in profound dementia and death, each person with dementia represents an approximately \$1 million expense to his or her family and to insurers. Ultimately, CTE and AD are likely to be preventable illnesses, but serious prospects for meaningful prophylaxis are at least a decade away. Half of the population over age 85 is demented now; by 2050, the annual cost of caring for dementia patients will exceed \$1 trillion. Therefore, if life-style modifications for *APOE* ε4 carriers—such as avoiding high-impact sports or opting for military careers that do not put the brain at risk—can reduce dementia prevalence in 2050 by even 1%, we would gain an annual savings of \$10 billion in costs of care—and immeasurable savings in terms of human suffering.

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Biographies

Sam Gandy

Steven T. DeKosky

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