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NEUROSCIENCE

Seeking tests for a contested brain disease

FDA warning to UCLA highlights struggle to diagnose chronic traumatic encephalopathy

By **Emily Underwood**

Tony Dorsett was always quick on his feet, nimbly evading many crushing collisions as a star running back for the Dallas Cowboys. Still, the former National Football League (NFL) player sustained numerous concussions during his 12-year career. Now, Dorsett believes he is paying for those hits.

Last year, several news outlets reported that after having his brain scanned at the University of California, Los Angeles (UCLA), Dorsett was told he shows signs of chronic traumatic encephalopathy (CTE), a neurodegenerative disease associated with repeated blows to the head. Along with several other former pro football players scanned at UCLA, the 61-year-old now attributes his failing memory and mood swings to CTE.

Dorsett's bombshell shocked the sports world—and alarmed many CTE researchers. Despite a widespread belief that the brain disorder is common among athletes in high-impact sports, there is no proven method of diagnosing CTE while a patient is alive, says Samuel Gandy, a neurologist at Mount Sinai Hospital in New York City. The medical literature lists only about 100 proven cases, all based on postmortem analysis of brain tissue. The scarcity of evidence, Gandy says, has fueled "controversy over what CTE is, and if it exists." Meanwhile, high-stakes lawsuits, including ones filed by former players against the NFL, have added to the pressure on researchers such as Gandy, who are struggling to come up with methods for diagnosing and tracking the disorder.

Last week, when CTE researchers met at a traumatic brain injury conference in Washington, D.C., to take stock of their fledgling field, they discussed some tantalizing leads. But hallway chatter centered on a new controversy. As first reported by the *Los Angeles Times* on 10 April, the U.S. Food and Drug Administration (FDA) in February ordered the doctor who delivered the bad news to Dorsett, UCLA psychiatrist Gary Small, to remove promotional language from the website of a company, TauMark, which has licensed his and colleagues' research into imaging a protein called tau. The company's site once displayed the slogan "Better Brain Diagnostics" and claimed that its PET scans could detect signs of CTE in living people. But those at the D.C. meeting agreed with FDA's conclusion that the company's message was misleading. "There are no diagnostic criteria for CTE in vivo," declared neurologist Douglas Smith of the University of Pennsylvania. "We need to clear the air."

> ***"There are no diagnostic criteria for CTE in vivo."***
>
> **Douglas Smith**, University of Pennsylvania

Only in the past month or so have researchers arrived at a consensus about what CTE looks like in postmortem brain tissue, Robert Stern, a neurologist at Boston University, told meeting attendees. Last month, eight neuropathologists convened to examine digital images of brain slices taken from people who had had a variety of neurodegenerative conditions, including Alzheimer's disease and suspected CTE. Blind to each sample's clinical diagnosis, the group identified two patterns that set CTE apart from other pathologies: clusters of a molecule called tau sequestered inside neurons that surround blood vessels in the brain; and clumps of tau in neurons and other brain cells at the bottoms of sulci, the folds that make up a human's wrinkly cortex. The group's findings, which will be presented at the American Academy of Neurology meeting in Washington, D.C., this week, are the first strong demonstration that CTE "is indeed a pathological disease that is unique," Stern says.

Small and his UCLA colleagues say they have found similarly located deposits of tau in living patients using their noninvasive technique. In a series of papers, including one online on 6 April in the *Proceedings of the National Academy of Sciences* (*PNAS*), they reported injecting former NFL athletes with a patented radioactive compound called FDDNP. The compound, originally designed to study β amyloid plaques in Alzheimer's

Former running back Tony Dorsett (33) was reportedly told that his football career had likely given him a neurodegenerative disease.

disease, binds to abnormal protein deposits in the brain and is visible under a PET scan. In the former players, it revealed a smattering of tau and amyloid protein deposits distributed in a pattern that resembles CTE pathology and can be reliably distinguished from the plaques and tangles found in Alzheimer's disease, the team reported.

Stern is not convinced, saying that the pattern of FDDNP-labeled areas that the UCLA team saw in the PET scans "is not consistent with the neuropathological findings" that came out of the consensus meeting in March. Because FDDNP binds to so many different substances in the brain, it is not an ideal compound for imaging tau's presence, adds Patrick Bellgowan, a program director at the National Institute of Neurological Disorders and Stroke (NINDS) in Bethesda, Maryland. The UCLA group stands by its findings, however, saying that FDDNP does not need to bind exclusively to tau in order to provide a reliable picture of CTE's progression and distinguish it from other neurodegenerative diseases.

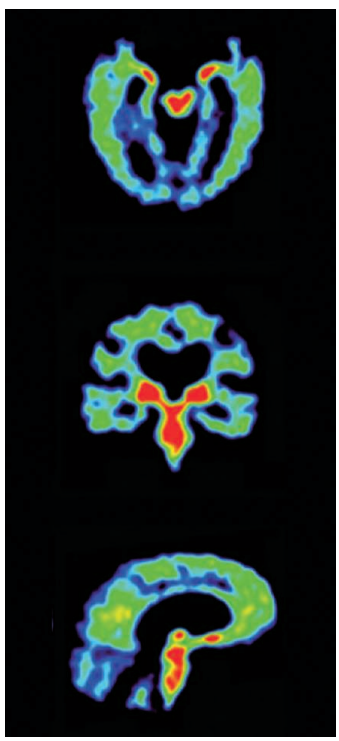
The *PNAS* report also raised eyebrows because its authors include Robert Fitzsimmons, a personal injury lawyer who in 1999 represented the late Hall of Fame center Mike Webster in a disability lawsuit against the NFL. Although Fitzsimmons is not involved in the class action suits, which involve more than 4000 former players, Webster was the first NFL player to be diagnosed with CTE after his death, and many credit his case with launching the current suit. In a statement, the UCLA team said that Fitzsimmons, who is a director at TauMark, "had significantly contributed to the design of this study because of his broad experience with concussions and brain damage." (He and two other co-authors on the *PNAS* paper founded the Brain Injury Research Institute in 1996.)

Despite the field's bumpy progress, Stern is convinced that diagnostic tools for CTE in living people are within reach. At the meeting, he presented preliminary PET data from former NFL players showing that T807, a compound that he says binds more specifically to tau than FDDNP does, detected deposits of the protein in the brain's cortical folds in a pattern similar to that seen in postmortem tissue. "I am confident that within the next five to ten years there will be highly accurate, clinically accepted, and FDA-approved methods to diagnose CTE during life," Stern wrote in an October 2014 affidavit to the lawsuit filed against the NFL by retired players.

The stakes are high for those players. Under the current settlement with the retired athletes, the NFL will compensate only those diagnosed with Alzheimer's disease or a "neurocognitive disorder," Stern says. A player who could receive $1 million if he has an Alzheimer's diagnosis, for example, might receive less than half that, or nothing all, because CTE can't yet be definitively diagnosed. The settlement is now in final negotiations, but as written it can be revised to incorporate new diagnostic criteria for CTE only every 65 years, Stern says.

Too much tau?

Brain scans of former NFL players highlight a disputed tag (red) for protein deposits.



The rush to find new diagnostic tools makes it easy to forget that research into CTE "is just at the starting line," Smith cautions. Tau deposits may only be a shadow or aftereffect of head injury, and not a cause of symptoms, for example. Fundamentally, Smith says, "we need to explore what shifts you from a normal aging track to a neurodegenerative track."

To tackle that question, scientists must follow large groups of people with concussions and other head injuries, ideally until they die and their brain tissue can be examined, Bellgowan says. Research groups funded by the NFL and NINDS are already looking for markers of CTE in blood samples and brain tissue from thousands of people enrolled in an ongoing study funded by the National Institute on Aging, he says. And Bellgowan adds that NINDS is reviewing a fresh round of grant proposals aimed at detecting CTE and defining its progression. The clock is ticking on Stern's prediction. ■

IMAGE: BARRIO *ET AL.*, *PNAS* **3** (6 APRIL 2015)

EUROPE

Plan for E.U. research funds raises ire

European Parliament vows to shield science budget from stimulus package raid

By **Tania Rabesandratana**

A battle has erupted in Brussels over the European Commission's plan to raid research funds in a bid to boost Europe's lagging economy. Announced in November, the plan involves diverting €2.7 billion from the European Union's 2014 to 2020 research budget to create a new E.U. investment fund. Member states like the idea, but scientists protested—and now the European Parliament appears to have heard them. Earlier this week, it voted to oppose raiding the research budget, setting the stage for lengthy negotiations with the Council of Ministers, which represents member states.

European Commission chief Jean-Claude Juncker and Carlos Moedas, the European Union's research commissioner, have insisted that researchers have no cause for alarm. First, the commission says the money diverted for the investment fund, known as the European Fund for Strategic Investments (EFSI), represents "only 3.5%" of the overall budget of Horizon 2020, the European Union's 7-year research funding plan. Second, the commission claims that the money will not be lost to science: "On the contrary, this is money that will be used to attract much more important sums [from national governments and private investors] that will then be reinvested in innovation," the commission said in a statement.

Scientists and research organizations don't buy this argument. Universities won't be able to use the money that is diverted, says the European University Association: Instead of supporting research grants, the funds would become seed capital for loans that many public organizations cannot use because they are not allowed to borrow money. Scientists are particularly incensed that the European Research Council, which distributes individual grants for fundamental research, would lose €221 million.