
We read with interest the recent article “TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy” by McKee et al (1). As neuromuscular specialists who care for large numbers of patients with amyotrophic lateral sclerosis (ALS), we have concerns about the conclusions drawn from 3 cases diagnosed as having ALS in life, while having histologic changes of both ALS and chronic traumatic encephalopathy (CTE) at autopsy.

In their 12-paragraph discussion section and subsequent New York Times interview (2), the authors propose a cascade of events starting with head trauma, leading to TDP-43 proteinopathy, and ultimately to various clinical phenotypes including motor neuron disease. In support of this, they state, “…of all the putative environmental risk factors, trauma to the CNS emerges as one of the strongest and most consistent contenders for initiating the molecular cascades that result in ALS.” In actuality, the data linking trauma to ALS are significantly flawed and controversial, and some experts have concluded that trauma is not a risk factor for ALS at all (3). Case 3 in the article had a sibling with ALS, raising the strong possibility that the cause of his disease was genetic. The coexistence of any motor neuron disease (MND) phenotype and CTE neuropathology in such a small number of cases could just be a chance association of 2 rare diseases. It is not surprising that high-level athletes who have experienced multiple head traumas will be found to have the neuropathologic features of CTE at autopsy. Nor is it surprising that patients with ALS have the typical pathological features of that disease, including TDP-43 proteinopathy. Oddly, the authors overlook their own observation that spinal cord tau immunoreactivity in the reported MND+/CTE+ Cases 4, 5, 6, 7, and 8 was equal to or greater than that of Case 2 (MND+/CTE+). This certainly argues against a causal relationship between tau (the supposed hallmark of CTE) and the development of at least this case of MND.

More disturbing still, the authors imply that their 3 cases and others (including Lou Gehrig himself) were “misdiagnosed” as having ALS when in fact they had a variant of CTE (2). Many patients have understandably been frightened and confused by these statements and are now wondering if their diagnoses are correct. The authors of this article should know that ALS is diagnosed by symptoms and clinical signs (4). Neither is brain and spinal cord biopsy part of the standard of care in making the diagnosis nor have the authors presented any convincing evidence that they should be. In the scant clinical information provided, we see no evidence that the 3 patients who had ALS along with CTE neuropathology progressed differently or responded differently to treatments compared with patients with more classic ALS neuropathology.

Finally, the authors state, “…if we can create this in laboratory mice, which are easily genetically altered and breed quickly, we can learn about the pathogenesis of this disorder and then provide treatment” (2). Aside from the above points questioning whether there even is a “this,” it is important to note that despite the fact that scientists have been studying several animal models of ALS subtypes (one for more than a decade), neither do we completely understand their pathophysiology nor, unfortunately, have we been able to use these models to improve treatment for the human disease. Someday, if the work of McKee et al can be confirmed in a much larger and better clinically characterized sample, another new subtype of ALS may be recognized, joining an ever-growing list. Until then, implied accusations of misdiagnoses and speculation on new MND subtypes (never mind their treatment) seem premature.

Richard S. Bedlack, MD, PhD
Duke University
Durham, North Carolina

Angela Genge, MD
McGill University
Montréal, Quebec

Canada

Anthony A. Amato, MD
Brigham and Women’s Hospital
Harvard Medical School
Boston, Massachusetts

Aziz Shaibani, MD
Baylor College of Medicine
Houston, Texas

Carlayne E. Jackson, MD
University of Texas Health Science Center
San Antonio, Texas

John T. Kissel, MD
Cheryl Wall, CNP
Wendy M. King, PT
Ohio State University
Columbus, Ohio

Edward Cupler, MD
Jau-Shin Lou, MD, PhD
Oregon Health Sciences University
Portland, Oregon

Erik Ensrud, MD
Baylor College of Medicine
Boston VA Medical Center
Boston, Massachusetts

Omer Tac, MD
Hacettepe University
Ankara, Turkey

Jonathan M. Goldstein, MD
Yale University School of Medicine
New Haven, Connecticut

Jonathan Katz, MD
Forbes Norris MDA/ALS Research Center
San Francisco, California

Mazen M. Dimachkie, MD
Richard J. Barohn, MD
University of Kansas Medical Center
Kansas City, Kansas
To the Editor:

We read with interest the article by McKee et al (1). The authors propose a novel disease that has been mistaken for ALS, and a new disease mechanism for the selective and progressive degeneration of motor neurons, all on the basis of findings in only 3 patients. The authors do not seem to have considered the possibility that they are seeing 2 conditions that are not causally related, but occurred together by chance, resulting in some pathological features. The lead author quoted in the article states that “Here he is, the face of his disease, and he may have had a different disease as a result of his athletic experience” (2). These sweeping generalizations go way beyond the evidence presented and have caused anxiety and confusion for patients and families struggling with the disease. Moreover, one of us (RGM) cared for 1 of the 3 patients who developed a pure motor degeneration of lower and upper motor neurons, with no change in cognition or any symptom to suggest CTE clinically. We appreciate this opportunity to provide detailed critique for publication where it can be linked directly to the original article (1).

Our first major concern is the presentation of the findings. It is hard to follow, hence difficult to interpret independently. The results are the patterns of distribution of tau-positive pathology and TDP-43–positive pathology in the brains (including brainstems) and spinal cords of patients with chronic traumatic encephalopathy (CTE) without motor neuron disease (MND), patients with CTE with MND, and patients with ALS. These pathological findings are virtually absent in controls.

Focusing first on the TDP-43 data, when CTE and ALS were present in the same patient (CTE/MND), the principal end-stage pathological findings are a summation of the findings in the individual conditions. A TDP-43 proteinopathy associated with CTE extending to involve the spinal cord, as hypothesized in the discussion of the article, would produce TDP-43 findings that are indistinguishable from those that would be expected owing to the chance occurrence of the 2 conditions in the same individual. It is our position that the evidence in the article does not provide a scientific basis for speculating a novel disease mechanism. Further, it is recognized that TDP-43 aggregation is not specific for a particular pathological process. It was present in some of the patients with CTE, but not all, and not to the same extent as in patients with ALS. On the basis of the study findings, TDP-43 aggregation is neither a necessary nor a sufficient condition for the development of CTE.

CTE is a 3R/4R tauopathy (1). The study showed that tau pathology in CTE is abundant in the brain and is seen occasionally in the spinal cord. Coexistence of CTE and ALS in these 3 patients resulted in an end-stage pattern of distribution of tau pathology in the spinal cord that was different from a direct summation of both conditions. Numerous tau-positive astrocytic tangles were seen surrounding degenerating anterior horn cells in 2 of 3 patients. As an end-stage observation, it cannot be used to infer the circumstance of disease onset or causality. We do not find it surprising that there is interaction between a preexisting process that tends to produce tau-positive tangles in the spinal cord and the surroundings of motor neurons dying because of ALS, resulting in greater abundance of the tangles. There is no basis in these findings to speculate that the death of the motor neurons was due to a new process mediated by the tau-positive tangles when we see the deposition of TDP-43–positive aggregates, the known process associated with ALS. A recent study reports that tau levels do not influence human ALS or motor neuron degeneration in the SOD1 G93A mouse (3). Furthermore, there are data suggesting strongly that the initial spread of ALS is mediated by upper motor neurons (4, 5). Terminal pathological findings within the spinal cord are unlikely to reflect the initiation of ALS.

In the Introduction, the authors present data on the role of trauma in ALS that do not acknowledge the epidemiologic controversies. The authors state that “Trauma to the CNS emerges as one of the strongest and most consistent contenders for initiating the molecular cascades that result in ALS” and cite 2 articles (6, 7) in support of that conclusion. Neither of the 2 articles makes that claim, and application of evidence-based methodology shows that neither provides a foundation for such an inference because both provide class 4 evidence that may not be relied on to draw conclusions (8). Chen et al (6) provided a primary analysis based on data gathered in a case-control study from 1993 to 1996 that has been the subject of 3 previous reports. These data showed an association that did not attain statistical significance between ever having a head injury and ALS. Secondary (exploratory) analysis showed an increased risk for individuals with more than one episode of head injury or with an injury within 10 years of disease onset. Acceptance of these findings is tempered by risks of recall bias, compounded by differences in the way cases were interviewed (in person) compared with controls (over the telephone) and likelihood that, when many analyses are performed on a large body of data, some associations may occur because of chance alone (class 4 evidence). Chen et al then did a meta-analysis of 8 studies, in 4 of which the head injury was “not specifically defined.” The meta-analysis showed a statistically significant association between head trauma and ALS. However, it is not appropriate to perform a meta-analysis with data from studies that do not provide high-quality evidence (8, 9). For this reason, the American Academy of Neurology does not use meta-analysis in its application of evidence-based methods. Most of the articles included were considered inadequate (8, 9) to lead to sound conclusions. The second reference cited by McKee et al is a case-control study in veterans (7). It did not show an association between head injuries and ALS in the primary analysis. In the secondary

REFERENCES

2. Schwarz A. Study says brain trauma can mimic ALS. New York Times August 17, 2010

Tahseen Mozaffar, MD
University of California Irvine
Orange, California