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ABSTRACT

Objective: The goal of this study was to examine the clinical presentation of chronic traumatic encephalopathy (CTE) in neuropathologically confirmed cases.

Methods: Thirty-six adult male subjects were selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy brain bank. Subjects were all athletes, had no comorbid neurodegenerative or motor neuron disease, and had next-of-kin informants to provide retrospective reports of the subjects' histories and clinical presentations. These interviews were conducted blind to the subjects' neuropathologic findings.

Results: A triad of cognitive, behavioral, and mood impairments was common overall, with cognitive deficits reported for almost all subjects. Three subjects were asymptomatic at the time of death. Consistent with earlier case reports of boxers, 2 relatively distinct clinical presentations emerged, with one group whose initial features developed at a younger age and involved behavioral and/or mood disturbance (n = 22), and another group whose initial presentation developed at an older age and involved cognitive impairment (n = 11).

Conclusions: This suggests there are 2 major clinical presentations of CTE, one a behavior/mood variant and the other a cognitive variant. *Neurology*® 2013;81:1122–1129

GLOSSARY

AD = Alzheimer disease; **CSTE** = Center for the Study of Traumatic Encephalopathy; **CTE** = chronic traumatic encephalopathy; **p-tau** = hyperphosphorylated tau; **RBT** = repetitive brain trauma; **TBI** = traumatic brain injury.

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease marked by widespread accumulation of hyperphosphorylated tau (p-tau).[1,2] To date, CTE has been documented in amateur and professional athletes involved in contact sports, military personnel exposed to explosive blast, and others subjected to repetitive brain trauma (RBT), including concussive and subconcussive injuries.[1–5] All reported neuropathologically confirmed cases of CTE have had exposure to RBT. However, not all individuals with histories of RBT develop CTE, indicating that additional risk factors, including genetics, likely have a role in the neuropathogenesis of this disease. For example, it has been suggested that the *APOE* ε4 allele may increase susceptibility for CTE.[6]

Previously published descriptions of the clinical presentation of CTE vary. Case reports of presumptive CTE (formerly termed dementia pugilistica or "punch-drunk" when thought limited to boxers[4]) indicated a constellation of clinical features, including impairments in cognition, behavior, and mood, and in some cases, chronic headache and motor and cerebellar dysfunction. Several case reports of boxers suggested 2 forms of presentation: 1) younger onset, with initial behavioral and mood disturbance, but with minimal cognitive and motor features; and 2) older onset, with greater cognitive impairment and, often, motor disturbance.[4,7–10] In advanced cases,

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CTE is associated with dementia, although it is unclear whether the clinical presentation of CTE dementia is different from that associated with Alzheimer disease (AD) or other age-related neurodegenerative disorders.[11–13] Herein, we describe the clinical presentation, course, and *APOE* genotype of a sample of 36 athletes with neuropathologically confirmed CTE.

METHODS **Subjects.** The brains of 81 subjects in the Boston University Center for the Study of Traumatic Encephalopathy (CSTE) brain bank met recently published criteria for the neuropathologic diagnosis of CTE.[1] For the current study, 45 cases were excluded because of 1) primary exposure to RBT from nonathletic activities; 2) inability to contact next-of-kin to conduct an interview; and 3) presence of comorbid motor neuron disease,[14] neurodegenerative disease, or other significant neuropathology. Seven were military veterans with unknown or no athletic history, 10 had no next-of-kin contact, and 28 had comorbid neuropathologic disease. Of the 36 remaining subjects, 28 were included in a previous report[1] and 8 were new cases.

CTE neuropathologic staging. The cases were categorized into the 4-stage rating scale of CTE (I = least severe, IV = most severe) based on the severity of p-tau pathology, as previously reported.[1] Diagnosis and staging were conducted blind to medical history, *APOE* genotype, and informant interview.

Interview and medical record review. History and clinical presentation were obtained through postmortem telephone interviews with next-of-kin by a neuropsychologist (R.A.S.) blinded to neuropathologic findings and *APOE* genotype status. Medical records were available and reviewed for 23 cases. The semistructured interview was based on previous studies of postmortem dementia diagnosis made by interviews with family members.[15,16] Information queried during the interview included the following: demographics; cause of death; and athletic, military, medical, neuropsychiatric, and social/occupational histories. The interview included specific questions regarding dementia, depression, changes in cognition, behavior, mood, and motor functioning, as well as instrumental activities of daily living. Responses were qualitatively summarized into an overall assessment of the subject's presentation and course of symptoms and functioning. The number of informants interviewed per case ranged from 1 to 7 (median = 2), with each interview lasting approximately 60 minutes. Interviews were conducted at a median time of 4 months after time of death.

***APOE* genotyping.** DNA was extracted from brain tissue samples using a Qiagen QIAamp DNA extraction kit (Qiagen, Valencia, CA). Two single nucleotide polymorphisms (National Center for Biotechnology Information SNPs rs429358 and rs7412) were examined using TaqMan assays (Applied Biosystems, Foster City, CA). Allelic discrimination was automated using the manufacturer's software. Positive controls, consisting of DNA of each of the 6 possible *APOE* genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4), were included on each plate and genotyped with restriction isotyping.

Statistical analyses. Between-group differences were examined by independent sample *t* tests. Chi-square analyses were used for between group comparisons for categorical data. *APOE* genotype analyses comparing CTE cases with population norms[17] were conducted with the χ^2 goodness-of-fit test. A probability level of $p = 0.05$ was used throughout. All statistical analyses were conducted with IBM SPSS Statistics, version 19.0 (IBM Corp., Armonk, NY).

Standard protocol approvals, registrations, and patient consents. Approvals for brain donation, postmortem clinical record review, interviews with family members, and neuropathologic evaluation were provided by the Institutional Review Boards of Boston University Medical Center and the Bedford VA Hospital.

RESULTS Table 1 summarizes the demographics, cause of death, athletic history, neuropathologic stage, and *APOE* genotypes of the sample. All subjects were male athletes, with 6 (17%) African American and 1 (3%) of Hispanic origin. There were 29 football players (22 who played professionally, 4 who only played through college, and 3 who only played through high school), 3 professional hockey players, 1 professional wrestler, and 3 boxers (1 professional, 2 amateur). Of the football players, the most common position played was lineman (48%), followed by running back (21%), linebacker (10%), and smaller numbers of other positions. There were no quarterbacks or kickers. Of the 36 subjects, 3 (8%) were asymptomatic. Tables 2 and 3 describe the clinical features and course of the remaining 33 subjects.

Eleven of the symptomatic cases were reported to have initial changes in cognitive functioning (e.g., episodic memory impairment, executive dysfunction) before behavioral or mood disturbance. Initial changes in behavior (e.g., explosivity, impulsivity, violence) before mood or cognitive disturbance were reported in 13 subjects. Mood changes (e.g., depression, hopelessness) were reported as the initial feature in 9 subjects. None of the subjects had motor disturbance as their initial feature. The subgroups with initial behavioral symptoms and mood changes were similar in age of initial presentation, age of death, and neuropathologic stage, and were combined into a behavior/mood group (n = 22). Subjects whose initial difficulties involved cognitive functioning comprised a cognition group (n = 11). Tables 1–3 describe demographics and clinical features for the behavior/mood and cognition subgroups.

Ten subjects were diagnosed with dementia; 4 were clinically diagnosed with AD, 4 with "dementia pugilistica" or "football-related" dementia, and 2 with unspecified dementia. All had stage IV CTE. Of the 10, 7 exhibited cognitive symptoms initially, 2 exhibited mood symptoms initially, and 1 initially presented with behavior changes. The mean age of symptom onset for the dementia group was 57.7 years (SD = 18.3; range 25–82) and the mean age of dementia diagnosis was 72.6 years (SD = 8.5, range 56–83). The mean length of time between dementia diagnosis and death was 8.0 years (SD = 5.5, range <1–15). Four subjects with dementia had gait difficulties, 3 had

Table 1 Description of sample by initial clinical presentation

Variable	All subjects (n = 36)	Behavior/mood group (n = 22)[a]	Cognition group (n = 11)[a]
Age at death, y, mean ± SD (range)	56.8 ± 21.9 (17–98)	51.4 ± 18.5 (21–84)[b]	69.2 ± 21.8 (34–98)[b]
Cause of death, %			
Systemic illness	41.8	49.8	27.3
Accidental overdose	13.9	18.2	9.1
Dementia-related	13.9	9.1	27.3
Suicide	16.7	18.2	18.2
Injury	8.4	4.5	18.2
Years of education, mean ± SD (range)	15.0 ± 2.4 (10–20)	14.5 ± 2.4 (10–18)	15.7 ± 1.4 (13–18)
Football as primary sport, %	80.6	72.7	90.9
Total years of football played, mean ± SD (range)	15.3 ± 6.4 (3–25)	14.4 ± 6.5 (3–25)	18.2 ± 5.9 (5–24)
Neuropathologic severity stage, %			
Stage I	8	9.1	0
Stage II	28	31.8	9.1
Stage III	31	31.8	36.4
Stage IV	33	27.3	54.5
APOE genotype,[c] %			
ε2/ε2	0	0	0
ε2/ε3	3	4.5	0
ε2/ε4	0	0	0
ε3/ε3	63	63.6	54.5
ε3/ε4	26	27.3	27.3
ε4/ε4	9	4.5	18.2

[a] Three subjects were asymptomatic; percentages within initial feature group are based on the percent of symptomatic subjects.
[b] Statistically significant between-group difference, $p < 0.05$.
[c] One subject did not have *APOE* genotyping.

a history of falls, and 1 had a history of tremor. Two subjects (20%) with dementia had a history of headaches, compared with 11 subjects (44%) without dementia. All 10 subjects had both memory and executive impairment, 7 had language deficits, and 2 had visuospatial difficulties. Six of the 10 were characterized by behavioral impairment, predominantly described as having a "short fuse" or being "out of control." Four of the 10 were physically violent and 2 were verbally violent. Although one subject demonstrated disinhibited behavior, none of the subjects had disinhibited speech or socially inappropriate behaviors. Of the 7 who were reported to have mood disturbance, 2 had predominantly sadness/depressive symptoms and 2 had anxiety symptoms. The only 2 subjects in the entire sample reported to have had apathy were in the dementia group.

The proportions of *APOE* genotypes (i.e., ε4 homozygotes, combined ε4 homozygotes and heterozygotes, and ε4 noncarriers) in our CTE sample were significantly different from those found in an age-matched normative sample[17] (χ^2 [2] = 6.63, $p < 0.05$). A binomial test revealed that the primary difference between our CTE sample and population norms was a greater proportion of ε4 homozygotes in our sample ($p < 0.05$). When examining the 2 initial presentation groups, there were no differences between the behavior/mood group and the age-matched normative sample (χ^2 [2] = 0.46, $p > 0.05$). However, there were proportionally more ε4 homozygotes in the cognition group than expected (χ^2 [2] = 13.3, $p < 0.05$). The relative proportions of *APOE* genotypes in our 10 subjects with dementia were not significantly different from those seen in AD[18] (χ^2 [2] = 1.52, $p > 0.05$).

DISCUSSION Consistent with earlier reports of boxers,[4,7–10] our findings suggest that there may be 2 different clinical presentations of CTE, with one initially exhibiting behavioral or mood changes, and the other initially exhibiting cognitive impairment. The behavior/mood group demonstrated symptoms at a significantly younger age than the cognition group. Although almost all subjects in the behavior/

Table 2 Clinical features and course by initial clinical presentation

Variable	All symptomatic subjects (n = 33)[a]	Behavior/mood group (n = 22)[a]	Cognition group (n = 11)[a]
Percent with progressive course	90.9	86.4	100
Percent with dementia diagnosis at death	30.3	18.2[b]	54.5[b]
Age first clinical feature observed, y, mean ± SD (range)	42.5 ± 17.8 (19–82)	34.5 ± 11.6 (19–59)[b]	58.5 ± 17.7 (31–82)[b]
Duration of clinical features, y, mean ± SD (range)	14.9 ± 12.9 (0–51)	17.0 ± 14.3 (0–51)	10.7 ± 8.5 (1–30)
Initial clinical domain, %			
Cognition	33.3	—	100
Behavior	39.4	59.1	—
Mood	27.3	40.9	—
Clinical domain(s) ever observed during life, %			
Cognition	93.9	90.9	100
Behavior	75.8	86.4[b]	54.5[b]
Mood	84.8	95.4[b]	63.6[b]
Motor	30.3	27.3	36.4
Cognition and behavior	75.8	86.4	54.5
Cognition and mood	81.8	90.9	63.6
Cognition and motor	30.3	27.3	36.4
Behavior and mood	72.7	86.4	45.5
Behavior and motor	27.3	27.3	27.3
Mood and motor	30.3	27.3	36.4
Cognition, behavior, and mood	72.7	86.4	45.5
Cognition, behavior, and motor	27.3	27.3	27.3
Cognition, mood, and motor	30.3	27.3	36.4
Behavior, mood, and motor	27.3	27.3	27.3
All 4 domains	27.3	27.3	27.3
History of significant headaches, %	34.4	38.1	27.3
Death by suicide, %	18.2	18.2	18.2
History of substance abuse, %	39.4	36.4	45.5

[a] Three subjects were asymptomatic; percentages are based on the percent of symptomatic subjects.
[b] Statistically significant, $p < 0.05$.

mood group demonstrated cognitive impairments at some point, significantly fewer subjects in the cognition group demonstrated behavioral and mood changes during the course of their illness. There were distinctions between the 2 groups regarding specific features present in each domain. The behavior/mood group was significantly more explosive, out of control, physically and verbally violent, and depressed than the cognition group. Whereas all subjects in the cognition group were reported to have impaired episodic memory, approximately one-quarter of the behavior/mood group did not have memory difficulties. Subjects in the cognition group were significantly more likely to progress to dementia than those in the behavior/mood group but were also significantly older at the time of death. Given the small sample size in this study, however, it is unclear whether these 2 apparently distinct clinical subtypes are representative of all individuals with CTE. In addition, the subsample of cases with dementia is also small, thus limiting the generalization of the presentation of CTE dementia. Further research is needed to clarify and validate these findings.

We examined the potential role of the *APOE* ε4 allele as a susceptibility factor for CTE. Our findings indicate that there were significantly more ε4 homozygotes in the sample than expected in a normal, age-matched population. Furthermore, this effect was largely driven by the cognition group: 2 of 11 subjects in the cognition group and 1 of 22 subjects in the behavior/mood group were homozygous for the ε4 allele. In addition, 1 of the 10 CTE subjects diagnosed

Table 3 Specific clinical features by initial clinical presentation

Variable	All symptomatic subjects, % (n = 33)	Behavior/mood group, % (n = 22)[a]	Cognition group, % (n = 11)[a]
Cognitive features			
Memory impairment	84.8	77.3	100
Executive dysfunction	78.8	72.7	90.9
Attention and concentration difficulties	72.7	63.6	90.9
Language impairment	57.6	54.5	63.6
Visuospatial difficulties	54.5	54.5	54.5
Behavioral features			
Explosivity	57.6	72.7[b]	27.3[b]
Impulse control problems	45.5	54.5	27.3
"Out of control"	51.5	63.6[b]	27.3[b]
Physically violent	51.5	68.2[b]	18.2[b]
Verbally violent	48.5	73.6[b]	18.2[b]
Disinhibited speech	0	0	0
Disinhibited behavior	3.0	0	9.1
Socially inappropriate	3.0	0	9.1
Paranoia	18.2	22.7	9.1
Mood features			
Sadness/depression	63.6	86.4[b]	18.2[b]
Anxiety/agitation	15.2	13.6	18.2
Manic behavior/mania	3.0	4.5	0
Suicidal ideation/attempts	30.3	31.8	27.3
Hopelessness	63.6	72.7	45.5
Apathy	6.1	9.1	0

[a] Three subjects were asymptomatic; percentages are based on the percent of symptomatic subjects.
[b] Statistically significant between-group difference, $p < 0.05$.

with dementia during life was ε4 homozygous. Although interpretation and generalization of these results is difficult because of the small sample, the proportion of ε4 homozygosity is in contrast to population norms in which ε4 homozygosity only occurs in 1% to 3% of the general population,[17] and more consistent with the 10% of patients with AD who are ε4 homozygous.[18] The *APOE* ε4 variant is the largest known genetic risk factor for sporadic AD.[18] It has been associated with β-amyloid, but not tau, deposition in cognitively normal aging.[19] *APOE* ε4 has also been associated with greater severity of cognitive deficits and longer recovery time after traumatic brain injury (TBI) and RBT in a variety of populations, including boxers and professional football players,[20–24] and may increase the risk of clinical dementia after TBI.[25] It has been hypothesized that the *APOE* ε4 isoform may have direct neurotoxic effects leading to mitochondrial dysfunction and cytoskeletal changes, resulting in increased risk of neurodegeneration.[26] Despite the small sample size and other limitations in the current study, future research on the role of *APOE* in CTE risk appears warranted. However, other potential susceptibility genes also merit consideration, including mutations to the microtubule-associated protein tau (*MAPT*) gene, the progranulin (*GRN*) gene, and the chromosome 9 open reading frame 72 (*C9ORF72*) gene. Moreover, additional nongenetic risk factors for CTE should be examined in future research, including studies to determine what specific aspects of RBT exposure (e.g., types, severity, frequency, initial age, and duration of trauma) are associated with CTE, as well as what potential lifestyle variables (e.g., diet, exercise, obesity, steroid use) are associated with the disease initiation and variability in presentation.

It is noteworthy that motor features, including parkinsonism, were not common in our sample. This is in contrast to some earlier descriptions of CTE in boxers, in which these motor features were quite prominent.[4] However, our findings are consistent with other case reports of predominantly younger onset boxers, in which motor disturbance was not common.[4,7–10] It is not clear why some individuals with CTE develop motor features and others do not. One possibility may be the differences in the biomechanics of injury. For example, in boxing, angular acceleration and torsional injury involving the brainstem and cerebellum is thought to be a pathogenic mechanism of TBI after a hook or jab to the jaw, whereas transverse and linear acceleration and deceleration injury are more characteristic of football dynamics.[27,28] As a result, degeneration of brainstem structures that produce parkinsonism, such as the substantia nigra, might occur earlier in the course of disease in boxers. In contrast, football players might develop substantia nigra degeneration later in the course of their disease, at a time when widespread cortical and basal ganglionic degeneration mask the development of motor disturbance. Related mechanisms of injury leading to CTE have been suggested by recent experimental studies of blast neurotrauma.[3]

Although many of the symptoms of CTE are similar to AD and other causes of dementia,[11,29] there are factors that appear to clinically differentiate CTE from other age-related neurodegenerative diseases. For example, behavioral changes observed early in the course of CTE could be confused with the behavioral variant of frontotemporal dementia, especially in a patient in his or her 50s without any significant memory impairment. However, common changes in the behavioral variant of frontotemporal dementia typically include disinhibited and inappropriate behavior and speech, as well as apathy[30]; these symptoms were not frequent in our case series. In addition, the progressive memory impairment observed in more than 80% of our CTE cases, and in all 10 of

the subjects with dementia, could lead to an inaccurate diagnosis of AD when the underlying disease is CTE.[12]

It is not clear what neuropathologic changes may lead to the 2 possible clinical presentations observed in this study. It is unlikely that the small, focal cortical p-tau lesions found in stage I and II CTE produce clinically meaningful behavioral and mood symptoms. However, these features may be associated with the neurofibrillary tangles in the locus coeruleus and amygdala found in younger subjects in a previous report.[1] The memory and executive dysfunction in the older cognition group may be due to the more extensive degenerative changes in the hippocampus and frontal cortices seen in CTE stages III and IV.[1] It is possible, however, that some of the features evident in the younger behavior/mood group were due to persistent postconcussion syndrome,[31] with unresolved or even progressive[32] axonal damage resulting from the initial traumas. Axonal injury has been shown in all neuropathologic stages of CTE, ranging from multifocal, perivascular axonal varicosities in the cortex and white matter in stages I and II, to more extensive, diffuse axonal loss in the cortex and white matter in stages III and IV.[1] Recent reports have demonstrated that repetitive subconcussive trauma is associated with white matter abnormalities on diffusion tensor imaging[33,34] and abnormal functional MRI tests.[35] Additional findings indicate that there may be persistent and progressive inflammation and white matter degeneration after even a single TBI.[36] Further research is required to delineate these clinicopathologic relationships.

Three subjects in our case series were asymptomatic. One of these cases was only 17 years old and had stage I neuropathology. Both of the other 2 cases were much older football players (one in 40s, one in 80s), had stage II neuropathology, and were homozygous for *APOE* ε3. Both also had advanced graduate degrees, were very successful in their professional careers, and were described as extremely intelligent. Although speculative, these findings raise the possibility that cognitive reserve[37] may have a role in protecting against the clinical manifestations of CTE. A recent report suggests that cognitive reserve may mitigate cognitive decline in older individuals with earlier life TBI.[38] Future research examining the roles of cognitive reserve, genetics, and environmental factors in determining resilience to clinical manifestations and the progression of p-tau pathology will help elucidate the pathobiology of CTE.

Although these findings are based on the largest cohort of subjects with neuropathologically confirmed CTE without comorbidities studied to date, interpretation and generalizability of these results are limited by several factors. First, the overall sample size is small, and caution should be taken when generalizing these results to the larger population of athletes or to the overall clinical presentation of CTE. In addition, there are inherent selection biases imposed in a postmortem brain donation study. For example, families choosing to donate may be more likely to have witnessed symptoms during life. This could lead to reports of more severe symptoms than a typical CTE population, and could account for only having 3 asymptomatic cases. From the broader CTE cohort in the CSTE brain bank, we selected a smaller sample by eliminating individuals with comorbid pathology and only including athletes; this restriction may further limit the generalizability of our findings. Results from this study should not be interpreted in terms of population prevalence or generalized to living athletes with CTE. In addition, there is the potential for reduced reliability and validity of retrospective reports from family members after the death of a loved one. However, several studies have demonstrated adequate reliability and validity of these verbal autopsies in a variety of patient populations, including those with dementia[15,16] and psychiatric disorders.[39] There also may be differences in the accuracy of informant reports when comparing younger and older subjects. That is, informants of older subjects were asked to recall early- or midlife events possibly resulting in reduced accuracy compared with the informants of younger subjects. Finally, there was no comparison group of former athletes without CTE. This may limit the ability to draw conclusions that the clinical presentation described is specifically due to the effects of CTE. In our available dataset of subjects whose tissue had been examined at the BU CSTE brain bank, there was not an adequate number of subjects without CTE to make such a comparison. For example, 34 of 35 former professional football players had neuropathologically confirmed CTE.[1] Future research is needed to clarify the clinical presentation of CTE. The development of biomarkers (e.g., blood, CSF, neuroimaging, and tau-specific radiotracers) will result in the ability to detect and diagnose CTE during life and subsequent studies of risk factors, epidemiology, and treatment.[40]

AUTHOR CONTRIBUTIONS

Dr. Stern was responsible for drafting the manuscript, study concept and design, and analysis and interpretation of data. He also conducted some of the statistical analyses and had a role in obtaining funding. Mr. Daneshvar participated in drafting the manuscript, as well as acquisition of data, statistical analysis, and interpretation of data. Ms. Baugh participated in drafting the manuscript, as well as study design and acquisition of data. Dr. Seichepine participated in drafting the manuscript, as well as analysis and interpretation of data. Mr. Montenigro participated in drafting the manuscript and in study design. Mr. Riley participated in revising the manuscript, study design, and acquisition of data. Mr. Fritts, Ms. Stamm, Mr. Robbins, and Ms. McHale participated in revising the manuscript and acquisition of data. Ms. Simkin participated in revising the manuscript as well as conducting the *APOE* genotyping. Dr. Stein and Dr. Alvarez participated in revising the

manuscript, as well as acquisition and analysis of neuropathologic data. Dr. Goldstein and Dr. Budson participated in revising the manuscript and interpreting the data. Dr. Kowall participated in revising the manuscript, interpreting the data, and obtaining funding. Mr. Nowinski participated in revising the manuscript, study concept, acquisition of data, and obtaining funding. Dr. Cantu participated in drafting the manuscript, study design and concept, interpreting data, and obtaining funding. Dr. McKee participated in drafting the manuscript, study design and concept, acquiring, analyzing, and interpreting clinical data, acquiring, analyzing, and interpreting the neuropathologic data, and obtaining funding.

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This Week's *Neurology*® Podcast

The complexities of acute stroke decision-making (See p. 1130)

This podcast opens and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the September 24, 2013, issue of *Neurology*. In the second segment, Dr. Brett Kissela talks with Dr. Michel Shamy about his paper on the complexities of acute stroke decision-making. Next, Dr. Roy Strowd reads our e-Pearl of the week about Adie's tonic pupil. Then, Dr. Brett Kissela focuses his interview with Dr. Lou Caplan on his medical education and contributions to the field of neurology, interactions with C. Miller Fisher, and advice to our younger listeners beginning their careers. Disclosures can be found at www.neurology.org.

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