

REVIEW ARTICLE

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury

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Abstract

Since the 1920s, it has been known that the repetitive brain trauma associated with boxing may produce a progressive neurological deterioration, originally termed *dementia pugilistica*, and more recently, *chronic traumatic encephalopathy* (CTE). We review 48 cases of neuropathologically verified CTE recorded in the literature and document the detailed findings of CTE in 3 professional athletes, 1 football player and 2 boxers. Clinically, CTE is associated with memory disturbances, behavioral and personality changes, parkinsonism, and speech and gait abnormalities. Neuropathologically, CTE is characterized by atrophy of the cerebral hemispheres, medial temporal lobe, thalamus, mammillary bodies, and brainstem, with ventricular dilatation and a fenestrated cavum septum pellucidum. Microscopically, there are extensive tau-immunoreactive neurofibrillary tangles, astrocytic tangles, and spindle-shaped and threadlike neurites throughout the brain. The neurofibrillary degeneration of CTE is distinguished from other tauopathies by preferential involvement of the superficial cortical layers, irregular patchy distribution in the frontal and temporal cortices, propensity for sulcal depths, prominent perivascular, periventricular, and subpial distribution, and marked accumulation of tau-immunoreactive astrocytes. Deposition of β -amyloid, most commonly as diffuse plaques, occurs in fewer than half the cases. Chronic traumatic encephalopathy is a neuropathologically distinct slowly progressive tauopathy with a clear environmental etiology.

Key Words: Athletes, Concussion, Dementia, Encephalopathy, Neurodegeneration, Tau protein, Traumatic brain injury.

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INTRODUCTION

During recent years, there has been increasing attention focused on the neurological sequelae of sports-related traumatic brain injury (TBI), particularly concussion. Concussion is a frequent occurrence in contact sports: 1.6 to 3.8 million sports-related concussions occur annually in the United States (1–3). Most sports-related head injury is minor, and although most athletes who have a concussion recover within a few days or weeks, a small number of individuals develop long-lasting or progressive symptoms. This is especially true in cases of repetitive concussion or mild TBI, in which at least 17% of individuals develop chronic traumatic encephalopathy (CTE) (4). The precise incidence of CTE after repetitive head injury is unknown, however, and it is likely much higher. It is also unclear what severity or recurrence of head injury is required to initiate CTE; no well-designed prospective studies have addressed these important public health issues (5–10).

Repetitive closed head injury occurs in a wide variety of contact sports, including football, boxing, wrestling, rugby, hockey, lacrosse, soccer, and skiing. Furthermore, in collision sports, such as football and boxing, players may experience thousands of subconcussive hits during the course of a single season (11, 12). Although the long-term neurological and neuropathologic sequelae associated with repetitive brain injury are best known in boxing, pathologically verified CTE has been reported in professional football players, a professional wrestler, and a soccer player, as well as in epileptics, head bangers, and domestic abuse victims (13–21). Other sports associated with a postconcussive syndrome include hockey, rugby, karate, horse riding, and parachuting (22–25), although the list is almost certainly more inclusive. Furthermore, additional large groups of individuals prone to repetitive head trauma, such as military veterans, may be at risk for CTE.

In this review, we present a summary of the 48 cases of neuropathologically verified CTE in the literature. We also report the clinical and immunocytochemical findings of CTE in 3 retired professional athletes, that is, 1 football player and 2 boxers, ranging in age from 45 to 80 years. Although the cases previously reported in the literature detailed some of the characteristic gross and histological features of CTE, the spectrum of unique regionally specific immunocytochemical abnormalities of phosphorylated tau

that occur in this disorder has not been previously described. We demonstrate that although CTE shares many features of other neurodegenerative disorders, including Alzheimer disease (AD), progressive supranuclear palsy (PSP), postencephalitic parkinsonism, and the amyotrophic lateral sclerosis/Parkinson-dementia complex of Guam (ALS/PDC), CTE is a neuropathologically distinct progressive tauopathy with a clear environmental etiology.

CLINICAL AND DEMOGRAPHIC FEATURES OF CTE

The concept of CTE was first introduced by Martland (26) in 1928, who introduced the term *punch-drunk* to a symptom complex that seemed to be the result of repeated sublethal blows to the head. This syndrome, long recognized in professional boxers, was termed *dementia pugilistica* by Millsbaugh (27) and the *psychopathic deterioration of pugilists* by Courville (28). The symptoms of CTE are insidious, first manifested by deteriorations in attention, concentration, and memory, as well as disorientation and confusion, and occasionally accompanied by dizziness and headaches. With progressive deterioration, additional symptoms, such as lack of insight, poor judgment, and overt dementia, become manifest. Severe cases are accompanied by a progressive slowing of muscular movements, a staggered propulsive gait, masked facies, impeded speech, tremors, vertigo, and deafness (27). Corsellis et al (29) described 3 stages of clinical deterioration as follows. The first stage is characterized by affective disturbances and psychotic symptoms. Social instability, erratic behavior, memory loss, and initial symptoms of Parkinson disease appear during the second stage. The third stage consists of general cognitive dysfunction progressing to dementia and is often accompanied by full-blown parkinsonism, as well as speech and gait abnormalities. Other symptoms include dysarthria, dysphagia, and ocular abnormalities, such as ptosis (29). The severity of the disorder seems to correlate with the length of time engaged in the sport and the number of traumatic injuries, although whether a single TBI can trigger the onset of CTE remains a matter of speculation.

Of the 51 neuropathologically confirmed cases of CTE, 46 (90%) occurred in athletes. The athletes included 39 boxers (85%) who fought as amateurs and as professionals for varying lengths of time (range, 4–25 years; mean, 14.4 years), 5 football players (11%) whose playing time ranged between 14 and 23 years (mean, 18.4 years; SD, 3.9), 1 professional wrestler, and 1 soccer player. The athletes began their respective sports at young ages, that is, between 11 and 19 years (mean, 15.4 years; SD, 2.2) (Tables 1 and 2). The first symptoms of CTE were noticed at ages ranging from 25 to 76 years (mean, 42.8 years; SD, 12.7). One third were symptomatic at the time of their retirement from the sport, and half were symptomatic within 4 years of stopping play. Common presenting symptoms included memory loss, irritability, outbursts of aggressive or violent behavior, confusion, speech abnormalities, cognitive decline, gait abnormalities, unsteadiness, headaches, slurred speech, and parkinsonism. In 14 cases (30%), there was a prominent

mood disturbance, usually depression (28%); 1 boxer was described as having a “euphoric dementia” (31); another boxer was described as manic-depressive (35); and a football player was considered “bipolar” (40). In most of the reported cases, the disease slowly progressed for several decades (range, 2–46 years; mean, 18.6 years; SD, 12.6), with increasing abnormalities in behavior and personality, memory loss, cognitive decline, and visuospatial difficulties. Movement abnormalities were eventually found in 41.2% subjects consisting of parkinsonism; staggered, slowed, or shuffled gait; slowed, slurred, or dysarthric speech; ataxia; ocular abnormalities; and dysphagia. As Critchley (42) noted in 1957, “once established, it not only does not permit reversibility, but ordinarily advances steadily, even though the boxer has retired from the ring.”

CTE in Football Players

Five football players, including our Case A, had neuropathologically verified CTE at autopsy. All died suddenly in middle age (age at death, 36–50 years; mean, 44.0 years; SD, 5.0) and were younger at the time of death compared with boxers with CTE (age at death, 23–91 years; mean, 60.0 years; SD, 15.2). The duration of symptomatic illness was also shorter in the football players (range, 3–10 years; mean, 6.0 years; SD, 2.9) compared with the boxers (range, 5–46 years; mean, 20.6 years; SD, 12.3). All 5 football players played similar positions: 3 were offensive linemen, one was a defensive lineman, and the other was a linebacker. In the football players, the most common symptoms were mood disorder (mainly depression), memory loss, paranoia, and poor insight or judgment (each found in 80%), outbursts of anger or aggression, irritability, and apathy (each found in 60%), confusion, reduced concentration, agitation, or hyperreligiosity (each found in 40%). Furthermore, 4 of the 5 experienced tragic deaths, that is, 2 from suicide (16, 17), one during a high-speed police chase (40), and another from an accidental gunshot while cleaning his gun (Case A). Case A exemplifies these clinical features.

Case A

A 45-year-old right-handed white man died unexpectedly as a result of an accidental gunshot wound to the chest while he was cleaning a gun. He was a retired professional football player who played football in high school, 3 years of college, and 10 years in the National Football League as a linebacker. According to his wife, he was concussed 3 times during his college football years and at least 8 times during his National Football League career; however, only 1 concussion was medically confirmed. He was never formally diagnosed as having postconcussive syndrome and never sought medical attention for residual cognitive or behavioral difficulties. There was no history of ever losing consciousness for more than a few seconds, and he never required being carried off the field or hospitalization.

At age 40 years, his family began to notice minor impairments in his short-term memory, attention, concentration, organization, planning, problem solving, judgment, and ability to juggle more than one task at a time. His spatial abilities were mildly impaired, and his language was unaffected.

TABLE 1. Demographic Information

Case No.	Reference	Sex	Sport/Activity	Age Sport Begun, years	Years of Play	Age at Onset Symptoms, years	Interval Between Retirement and Symptoms, years	Interval Between Symptom Onset and Death, years	Age at Death, years	ApoE Genotype
1	30	M	Boxing	17	11	38	10	13	51	
2	31	M	Boxing	15	14	36	6	12	48	
3	32	M	Boxing	14	10	46	10	7	53	
4	32	M	Boxing	18	6	48	24	10	58	
5	28	M	Boxing		4				49	
6	33	M	Boxing							
7	33	M	Boxing							
8	34	M	Boxing	16	7	25	1	33	58	
9	35	M	Boxing	12	12	30	6			
10	35	M	Boxing	15	20	36	0	10	46	
11	35	M	Boxing	19	12	31	0	15	46	
12	35	M	Boxing	16	16	40	8	5	45	
13	35	M	Boxing	15	13	28	0	16	44	
14	35	M	Boxing	12	12		4		28	
15	29	M	Boxing	11	14	25	0	38	63	
16	29	M	Boxing		20	50	20	27	77	
17	29	M	Boxing	16	14	30	0	33	63	
18	29	M	Boxing	15	25	35	0	34	69	
19	29	M	Boxing	18	18	36	0	25	61	
20	29	M	Boxing	13	25	37	0	46	83	
21	29	M	Boxing	16	20	54	18	8	62	
22	29	M	Boxing	17	23	60	20	11	71	
23	29	M	Boxing		>10	31	0	41	72	
24	29	M	Boxing			40		27	67	
25	29	M	Boxing			48		19	67	
26	29	M	Boxing	14	16	43	4	14	57	
27	29	M	Boxing	18	10				61	
28	29	M	Boxing						91	
29	29	M	Boxing						58	
30	18	F	Physical abuse						76	
31	14	F	Autistic head banging						24	
32	36	M	Boxing		>25				63	
33	36	M	Boxing		>25				69	
34	19	M	Circus clown		15				33	
35	15	M	Boxing		>11	61	37	10	71	
36	13, 37	M	Boxing	11	12				23	ε3/ε4
37	13	M	Boxing	16	5		0		28	
38	13	M	Head banging						28	
39	13	M	Epilepsy						27	
40	13	M	Soccer						23	ε3/ε3
41	38	M	Boxing		10	64			67	ε3/ε4
42	39	M	Boxing			76			78	
43	17	M	Football	16	22				50	ε3/ε3
44	16	M	Football	18	14	35	2	10	45	ε3/ε3
45	21	M	Football	15	23	38	0	6	44	ε3/ε4
46	20	M	Wrestling	18	22	38	0	2	40	ε3/ε3
47	40	M	Football	16	17	36	3	3	36	
48	41	M	Boxing	16	17	58		13	61	ε3/ε3
49	Case A	M	Football	16	16	40	9	5	45	ε4/ε4
50	Case B	M	Boxing	17	5	63	33	17	80	ε3/ε4
51	Case C	M	Boxing	11	22	58	25	15	73	ε3/ε3

F, female; M, male.

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TABLE 2. Clinical Manifestations

Case No.	Initial Symptoms	I. Personality/Behavior Change	Dysphoria	Irritability	Confusion	Agitation	Paranoia
1	Memory, speech	x				x	
2	Euphoria, dementia	x	x				
3		x		x			x
4	Memory, confusion	x	x	x	x		
5	Memory, confusion	x			x		
6							
7							
8	Cognitive decline, hemiparesis	x	x	x	x		x
9	Manic-depressive psychosis	x	x				
10	Headaches	x	x		x		x
11	Headaches	x	x		x		
12	Slurred speech, gait change	x	x		x		
13	Punchy, unsteady						
14							
15	Violent outbursts	x		x			
16	Staggered gait, slowed speech	x		x	x		
17	Confusion, falls	x		x	x	x	x
18	Unsteadiness						
19	Irritability, memory loss, aggression	x		x			
20	Gait, speech	x					x
21	Dysphoria, violence	x			x		
22	Ataxia, falls, weakness				x		
23	Tremor, slurred speech	x					
24	Memory loss	x			x	x	x
25	Confusion	x			x		
26	Speech, delirium	x			x		x
27	None						
28	Aggression	x					
29	None						
30							
31							
32		x	x				
33		x	x				
34		x					
35							
36							
37	Paranoid schizophrenia						
38							
39							
40							
41	Cognitive decline, ALS-like syndrome	x		x	x	x	x
42	Cognitive decline, parkinsonism						
43	Memory, dysphoria	x	x				
44	Depression, erratic	x	x	x		x	x
45	Headaches, poor decisions	x	x				x
46	Depression, violent	x	x				
47	Bipolar disorder	x	x	x	x	x	x
48	Memory loss						
A*	Memory, confusion	x	x	x	x		x
B*	Disorientation, confusion	x		x	x	x	x
C*	Memory	x	x	x	x	x	x

*New Cases A, B, and C of this series.

x, clinical feature was noted as present; blank, clinical feature was not mentioned.

ALS, amyotrophic lateral sclerosis.

TABLE 2. (Continued)

Reduced Concentration	Aggression/ Violence	Poor Insight/ Judgment	Apathy	Hypersexuality	II. Somatic Symptoms	Headache	Dizziness	Insomnia
	x	x						
x	x				x	x		x
x	x				x	x		x
	x							
	x							
	x							
	x							
	x							
	x							
	x							
	x							
	x							
	x							
	x							
	x							
	x	x						
	x							
	x							
x	x	x						
		x						
x	x	x						
		x	x					
x	x				x			
x	x	x	x					
x	x	x						
x	x	x	x				x	

TABLE 2. (Continued)

Case No.	Deafness	Epilepsy	III. Cognitive Changes	Memory Loss	Dementia	Visuospatial Abnormalities	IV. Movement Abnormalities	Parkinsonism	Decreased Facial Movement
1			x	x	x		x	x	
2		x	x	x	x		x	x	
3			x	x			x		
4			x	x	x				
5			x						
6									
7									
8		x	x	x	x		x	x	x
9									
10									
11			x	x			x	x	
12			x	x					
13			x						
14							x	x	
15			x	x			x	x	
16			x	x	x		x		
17			x	x				x	x
18			x	x	x		x	x	
19			x	x					
20			x	x			x	x	
21			x	x	x		x		
22			x				x	x	
23			x	x	x		x	x	x
24			x	x	x				
25			x	x	x				
26			x	x	x		x	x	
27									
28									
29									
30									
31									
32			x	x			x	x	x
33			x	x			x	x	x
34			x	x	x				
35			x	x	x				
36									
37									
38									
39									
40									
41			x	x	x		x	x	x
42			x	x	x		x	x	
43			x	x	x		x	x	
44									
45			x	x					
46			x	x					
47			x	x	x				
48			x	x		x			
A*			x	x		x			
B*			x	x	x	x	x		
C*			x	x	x	x	x	x	x

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TABLE 2. (Continued)

Slowed Movements	Tremor	Rigidity	Falls	Ocular Abnormalities	Ptosis	Reduced Upgaze	Gait Problems	Staggered
x	x			x		x	x	
			x				x	
x							x	
				x			x	
					x		x	x
	x		x				x	x
	x	x	x				x	x
x							x	
							x	x
	x		x				x	
	x	x	x				x	
x								
							x	
	x						x	
	x							
							x	
			x				x	x
	x			x		x	x	

TABLE 2. (Continued)

Case No.	Slowed	Shuffled	Ataxia	Reduced Coordination	Speech Changes	Slowed	Slurred	Dysarthria	Dysphagia	Spasticity
1					x	x				
2			x							x
3			x							x
4										
5										
6					x					
7		x						x		x
8										
9			x		x		x	x		
10					x		x			
11				x	x	x				
12				x	x					
13										
14			x		x					
15			x		x	x	x			
16			x		x	x	x	x	x	x
17		x	x		x		x	x		x
18										
19	x	x	x		x		x	x		
20			x							
21			x		x					
22			x				x	x		
23										
24										
25					x	x	x			
26										
27										
28										
29										
30										
31					x			x		
32					x			x		
33			x							
34										
35										
36										
37										
38										
39										
40					x					x
41										
42										
43										
44										
45										
46										
47										
48										
A*										
B*					x		x			
C*	x	x			x		x			

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He repeatedly asked the same questions over and over, he did not recall why he went to the store unless he had a list, and he would ask to rent a movie that he had already seen. These symptoms gradually increased and became pronounced by the end of his life 5 years later. Using a modification of the Family Version of the Cognitive Difficulties Scale (43, 44), he had a moderate amount of cognitive difficulties. On a modified AD8 informant interview for dementia, he received a total score of 4, which indicated "cognitive impairment is likely to be present" (45). By contrast, the Functional Activities Questionnaire (46), an informant-based measure of instrumental activities of daily living, did not indicate significant functional dependence despite his difficulty in assembling tax records, shopping alone, and understanding television (total Functional Activities Questionnaire score, 3). Moreover, he continued to perform his job as a hunting and fishing guide in a satisfactory manner.

Toward the end of his life, he tended to become angry and verbally aggressive over insignificant issues and was more emotionally labile. He also began to consume more alcohol but did not show other signs or symptoms of depression. He had no significant psychiatric history, and he had never taken performance-enhancing or illicit drugs. His family history was negative for dementia and psychiatric illness.

CTE in Boxers

Boxing is the most frequent sport associated with CTE, and disease duration is the longest in boxers, with case reports of individuals living for 33, 34, 38, 41, and 46 years with smoldering, yet symptomatic, disease (29). Boxers with long-standing CTE are frequently demented (46%) and may be misdiagnosed clinically as AD (47), as occurred in Cases 2 and 3.

Case B

An 80-year-old African American/American Indian man was first noted to have difficulty remembering things in his mid-20s. He began boxing when he was 17 years old, quickly rose to professional ranks, and fought professionally for 5 years until he retired at age 22 years. He had a mild head injury in his early teenaged years while moving farm equipment, although he did not lose consciousness or experience any permanent disability. By his mid-30s, he had brief occasional episodes of confusion and a tendency to fall. His wife attributed his occasional forgetfulness, falls, and confusion to being mildly "punch-drunk." His symptoms remained more or less stable during the following 4 decades except for an increased tendency to become disoriented when traveling to unfamiliar places. By age 70 years, he got lost driving on familiar roads; he became increasingly confused and disoriented and did not recognize his daughter. By age 78 years, he was paranoid, his memory loss had increased, his gait was unsteady, his speech slowed, and he frequently fell. He was easily agitated and required multiple hospitalizations for aggressive behaviors. He died at age 80 years of complications of septic shock.

He had a period of alcohol abuse as a young adult but was abstinent for the last 40 years of his life. He smoked cigarettes for 20 years. He was employed as a roofer for most

of his life and was in excellent physical condition, running miles and doing daily calisthenics. He had no history of depression or anxiety and was generally pleasant and even-tempered. His family history was positive for a paternal grandfather with a history of cognitive decline and a brother with AD. Cerebral computerized axial tomography performed 2 and 3 years before death revealed progressive cerebral and cerebellar atrophy and mild ventricular enlargement.

Case C

A 73-year-old white man began boxing at the age of 11 years and fought as an amateur boxer for 9 years and as a professional boxer for 13 years. He fought a total of 48 professional bouts, accumulating 2 world championships before retiring at the age of 33 years. In his late 50s, he became forgetful with mood swings and restlessness. He changed from his normally happy easy-going self to become apathetic, socially withdrawn, paranoid, irritable, and sometimes violently agitated. During the next 2 years, he began to confuse close relatives and developed increasing anxiety, aggression, and agitation; on occasion, he was verbally abusive toward his wife and tried to strike her. He required neuroleptics for control of his behavior. The following year, he had episodes of dizziness, which was suspected to be vertigo, and resulted in a hospital admission. Neurological examination found him to be disoriented, inattentive, with very poor immediate and remote memory, and impaired visuospatial skills. Neuropsychological testing showed deficits in all cognitive domains, including executive functioning, attention, language, visuospatial abilities, and profound deficits in learning and memory. Computed tomographic scan and magnetic resonance imaging (MRI) showed generalized cortical atrophy, enlargement of the cerebral ventricles, cavum septum pellucidum, and a right globus pallidus lacuna. An electroencephalogram, an MR angiogram, and a carotid ultrasound were normal. He smoked and drank alcohol occasionally until his early 50s. A first cousin developed dementia in her early 50s, and 3 uncles and 1 aunt (of 11 children) were demented.

During the following 2 years, he continued to decline in all cognitive domains. He frequently fell and developed a tremor of his left hand. Repeat neuropsychological testing at age 67 years revealed further global deficits, again with prominent impairments in memory. By age 70 years, he had severe swallowing difficulties, diminished upgaze, masked facies, garbled speech, and a slow shuffling gait. Mini-Mental Status Examination several months before death was 7 out of 30. He died at the age of 73 years of complications of pneumonia.

CTE in Other Sports and Activities

Other sports associated with neuropathologically verified CTE are professional wrestling (20) and soccer (13). The first known case of CTE in a professional wrestler involved a 40-year-old white man who began professional wrestling at age 18 years and wrestled for the next 22 years (20). He was known for his rough aggressive style and had experienced numerous concussions and a cervical fracture during his career. At age 36 years, he began to experience problems in

TABLE 3. Gross Pathological Features: Atrophy

Case No.	Brain Weight, g	Thickened Leptomeninges	Atherosclerosis	Arteriosclerosis	Cerebral Atrophy	Frontal Lobe	Parietal Lobe	Temporal Lobe	Occipital Lobe
1		++	0	++	+				
2					+				
3	(Biopsy)								
4						+++			
5	1,120	+	0			+	+		
6									
7									
8	1,180				+				
9		+	++	++	+	+			
10		+	++	++					
11		+	+						
12		+	+						
13		+	+						
14		+	+						
15	1,310	++	+						
16	960		+	++	+++	+++		+++	
17	1,260								
18	1,205	+			+	+			
19	1,095	+				++		++	
20	1,300	+				0	0	0	0
21	1,090	+							
22	1,040					+++		+++	
23	1,435								
24	1,095								
25	1,030								
26									
27	950					+			
28	1,395								
29									
30						+			
31									
32						+			
33									
34	1,833		0						
35						+	+	+	
36									
37									
38									
39	(Lobectomy)								
40									
41						+		+	
42								+	
43	1,565					0	0	0	0
44									
45	1,535					0	0	0	0
46	1,510					0	0	0	0
47									
48						++		++	
A*	(Fragments)	0	0	0	0	0	0	0	0
B*	1,360	0	0	++	+	+	+	+	0
C*	1,220	+	+	+	++	++	++	++	+

*New Cases A, B, and C of this series.
 0, feature not present; +, mild; ++, moderate; +++, severe; blank, feature was not mentioned.

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TABLE 3. (Continued)

Hippocampus	Entorhinal Cortex	Amygdala	Mammillary Bodies	Thalamus/Hypothalamus	Brainstem	Cerebellum	Olfactory Bulb	Corpus Callosum
			+	+	+			
			+	+	+	+		+
			+	+	+	+		+
				+	+	+	+	+
					+	+		+
				+	+			+
			+					+
							+	
				+		+++		++
0	0	0						
+++	+++	+++	++	+	0	0	0	+
+++	+++	+++	++	++	0	0	+	+

his marriage, with periods of depression and lapses of memory. During his 40th year, he had episodes of violent behavior; he ultimately killed his wife and son and committed suicide. He was believed to have used anabolic steroids and prescription narcotics. His medical history included a motor vehicle accident at age 6 years requiring 3 days of hospitalization for mild TBI without known neurological sequelae.

Geddes and colleagues (13) reported finding mild changes of CTE in a 23-year-old amateur soccer player who regularly “headed” the ball while playing and had a history of a single severe head injury. Williams and Tannenberg (19) reported the findings of CTE in a 33-year-old achondroplastic dwarf, with a long history of alcohol abuse, who worked for 15 years as a clown in a circus. He had been knocked unconscious “a dozen times” and participated in dwarf-throwing events.

PATHOLOGICAL FEATURES OF CTE

Gross Pathology

In their comprehensive description of the pathology, Corsellis and colleagues (29) summarized the most common gross neuropathologic findings including 1) a reduction in brain weight, 2) enlargement of the lateral and third ventricles, 3) thinning of the corpus callosum, 4) cavum septum pellucidum with fenestrations, and 5) scarring and neuronal loss of the cerebellar tonsils. The reduction in brain weight is generally mild (mean, 1261 g; range, 950–1,833 g) and associated with atrophy of the frontal lobe (36%), temporal lobe (31%), parietal lobe (22%), and less frequently, occipital lobe (3%) (Tables 3–6). With increasing severity of the disease, atrophy of the hippocampus, entorhinal cortex, and amygdala may become marked. The lateral ventricles (53%) and III ventricles (29%) are frequently dilated; rarely, there is dilation of the IV ventricle (4%). Cavum septum pellucidum is often present (69%), usually with fenestrations (49%). Other common gross features include pallor of the substantia nigra and locus caeruleus, atrophy of the olfactory bulbs, thalamus, mammillary bodies, brainstem, and cerebellum, and thinning of the corpus callosum. Many of these gross pathological features were found in our Cases B and C.

Case B

The brain weighed 1,360 g. There was a mild yellow-brown discoloration in the leptomeninges over the temporal poles. There was mild atrophy of the frontal, parietal, and temporal lobes, most pronounced in the temporal pole. The floor of the hypothalamus was thinned and translucent, and the mammillary bodies were atrophic. The medial thalamus was atrophic and concave. The frontal, temporal, and occipital horns of the lateral and third ventricles were enlarged, with a 0.5-cm cavum septum pellucidum. The corpus callosum was thinned in its midportion. The anterior hippocampus, amygdala, and entorhinal cortex were severely atrophic. By contrast, the posterior hippocampus was only mildly atrophic. The substantia nigra and locus caeruleus were markedly pale.

Case C

The brain weighed 1,220 g. There was moderate atrophy of the frontal, parietal, and temporal lobes, most pronounced in the temporal pole. The floor of the hypothalamus was markedly thinned, and the mammillary bodies were atrophic. The corpus callosum was thinned, most prominently in its anterior portion. There was a large cavum septum pellucidum (0.8 cm) with fenestrations. The frontal and temporal horns of the lateral ventricles and the third ventricle were moderately enlarged. The entorhinal cortex, hippocampus, and amygdala were markedly atrophic throughout their entire extent. The medial thalamus was atrophic and concave. The perivascular spaces of the temporal and frontal white matter were prominent. A 1.0-cm lacuna was present in the internal segment of the right globus pallidus. There was severe pallor of the substantia nigra and locus caeruleus, with discoloration and atrophy of the frontopontine fibers in the cerebral peduncle.

See the appendix for methods of analysis for Cases A to C.

Microscopic Pathology

Neuronal Loss

A few reports in the literature (Cases 3, 4, 10, 12, 14, 29; Table 5) described neuronal loss and gliosis in the hippocampus, substantia nigra, and cerebral cortex without appreciable neurofibrillary pathology. Neuronal loss and gliosis most commonly accompany neurofibrillary degeneration, however, and are pronounced in the hippocampus, particularly the CA1 and subiculum, the entorhinal cortex, and amygdala. If the disease is advanced, neuronal loss is also found in the subcallosal and insular cortex and to a lesser degree in the frontal and temporal cortex. Other areas of neuronal loss and gliosis include the mammillary bodies, medial thalamus, substantia nigra, locus caeruleus, and nucleus accumbens. In Cases B and C, the cerebral cortex showed mild neuronal loss in the insular and septal cortices and moderate neuronal loss in the entorhinal cortex, amygdala, medial thalamus, mammillary bodies, substantia nigra pars compacta and pars reticulata, and to a lesser extent, locus caeruleus. In Case B, CA1 of the hippocampus showed moderate loss of neurons, and in Case C, CA1 and the subiculum of the hippocampus showed severe neuronal loss and gliosis.

Tau Deposition

Neurofibrillary tangles (NFTs), astrocytic tangles, and dotlike and spindle-shaped neuropil neurites (NNs) are common in the dorsolateral frontal, subcallosal, insular, temporal, dorsolateral parietal, and inferior occipital cortices. The tau-immunoreactive neurofibrillary pathology is characteristically irregular in distribution with multifocal patches of dense NFTs in the superficial cortical layers, often in a perivascular arrangement. This superficial distribution of neocortical NFTs was originally described by Hof and colleagues (47), who noted that the NFTs in CTE were preferentially distributed in layer II and the upper third of layer III in neocortical areas and generally more dense than in AD.

Geddes and colleagues (13, 37) drew attention to the perivascular distribution of NFTs in their description of the

TABLE 4. Gross Pathological Features: Other

Case No.	II Ventricle Enlarged	III Ventricle Enlarged	IV Ventricle Enlarged	Cavum Septum	Fenestrations	SN Pallor	LC Pallor
1	+	+					
2	+			+			
3							
4	+++						
5	+	+					
6				+			
7				+			
8				+		+++	
9	+			+	+		
10	+			+	+		
11	+			+			+
12	+			+			
13	+			+	+		
14	+			+			
15	++	++		+++	+	++	
16	+++	+++	+++	+++	+	++	
17	++	++		++	+	+++	
18	++	++		+	+	+++	
19	++	++	+	+++	+	+	
20	++	++		++	+	+++	
21	++	++		++	+		
22	++	++	+	++	+		
23	++			++	+	+++	
24	+++	+++		+++	+		
25	++			+++	+		
26	+			+			
27	++	++		++	+		
28	++	++		++			
29				+	+		
30				+++	+		
31				+++			
32				+	+		
33							
34	+++	+++			+		
35					+		
36				0	0	0	
37				0	0	0	
38				0	0	0	
39							
40				0	0	0	
41				+		++	++
42				+			
43						+	
44							
45				+			
46							
47							
48	++			+	+		
A*		+				0	0
B*	+	+		+	+	+++	+++
C*	++	++		++	+	+++	+++

*New Cases A, B, and C of this series.
 0, feature not present; +, mild; ++, moderate; +++, severe; blank, feature was not mentioned.
 LC, locus caeruleus; SN, substantia nigra.

TABLE 5. Microscopic Pathological Features: Neuronal Loss

Case No.	Frontal Cortex	Parietal Cortex	Temporal Cortex	Occipital Cortex	Hippocampus	Entorhinal Cortex	Amygdala	Cerebellum
1								
2								
3	+++	+++	+++					
4	+++	+++	+++					
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15	+							
16	+++	+++	+++					
17								
18								
19								
20	+	+	+	+				
21								
22	+	+	+	+				
23	+	+	+	+				
24								
25								
26	+++	+++	+++	+++				
27								
28								
29								
30								
31								
32								
33								
34								
35								
36								
37								
38								
39								
40								
41								
42								
43								
44								
45								
46								
47								
48	++	++	++	++	++			
A*	0	0	0	0	+	+	+	
B*	+	+	+	+	++	++	++	
C*	++	++	++	++	+++	+++	+++	

*New Cases A, B, and C of this series.
 0, feature not present; +, mild; ++, moderate; +++, severe; blank, feature was not mentioned.

TABLE 6. Microscopic Pathological Features: Other

Case No.	NFT										
	Frontal	Parietal	Temporal	Occipital	Thalamus	Hypothalamus	Septal Nuclei	Globus Pallidus	Caudate/ Putamen	Nucleus Basalis of Meynert	Mammillary Bodies
1	+	+	+	+							
2	+	+	+		+	+					
3											
4											
5	+	+	+								
6	+	+	+								
7	+	+	+								
8	+		+	+							
9											
10											
11	+	+	+								
12											
13	+	+	+								
14											
15	+										
16	+++	+++	+++								
17	+	+	+								
18	+++		+++								
19	+++	+++	+++	+++							
20	+	+	+								
21	+	+	+	+							
22	++	++	++	++							
23	++	++	++	++							
24			+								
25			+								
26	+++	+++	+++	+++							
27											
28	+	+	+	+							
29											
30	++	+	+								
31		++									
32	+		+							+	
33			+								
34			+								
35											
36			+								
37			+								
38			+								
39			+								
40			+								
41	++		+					++	++		
42	+		+								
43	+	+	+								
44	+		+								
45	+++		+++	++	+				+		++
46	+	+	+					+	+		
47											
48	++	++	++	0							
A*	+++	++	+++	++	+	+++	+++	0	+	+++	+++
B*	+++	+++	+++	++	++	+++	+++	+	++	+++	+++
C*	+++	+++	+++	++	+++	+++	+++	+	++	+++	+++

*New Cases A, B, and C of this series.
 0, feature not present; +, mild; ++, moderate; +++, severe; blank, feature was not mentioned.
 Aβ, β-amyloid; LC, locus caeruleus; NFT, neurofibrillary tangles; SN, substantia nigra; SP, senile plaques.

TABLE 6. (Continued)

Case No.	NFT											
	Hippocampus	Entorhinal Cortex	Amygdala	Periventricular Gray	Midbrain Tegmentum	SN	LC	Basis Pontis	Medulla	Inferior Olive	Red Nucleus	Cranial Nerves 3, 4 Nuclei
1	+++											
2	+++					+++						
3												
4												
5												
6												
7												
8	+++	+++	+++	+++	+++	+++	+++					
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
19												
20												
21												
22												
23												
24												
25												
26												
27												
28												
29												
30	+					+						
31												
32						+	+					
33						+						
34	+											
35	+			+		+	+					+
36	0											
37	0											
38	0											
39	0											
40	0											
41	+++											
42	+++											
43	0											
44	++	++				+	+	+	+			
45	++	++	++	+	+	++	++	+++	++			
46						+	+					
47												
48	+++					+	+					
A*	++	+++	++	+	+	++						
B*	+++	+++	+++	++	++	+++	+++	+	+	+	+	+
C*	+++	+++	+++	++	++	+++	+++	++	++	++	++	++

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neuropathologic alterations in the brain and frontal lobectomy specimens of 5 young men, ranging in age from 23 to 28 years. The 5 cases included 2 boxers, a soccer player, a person described as “mentally subnormal” with a long history of head banging, and a patient with epilepsy who frequently hit his head during seizures. Microscopically, all the brains showed argyrophilic tau-positive neocortical NFTs, strikingly arranged in groups around small intracortical blood vessels, associated with neuropil threads and granular tau-positive neurons. There were also NFTs along the basal surfaces of the brain, usually at the depths of sulci. The hippocampi of the 4 autopsy cases were normal.

In CTE, tau-immunoreactive protoplasmic astrocytes are interspersed throughout the superficial cortical layers appearing as plaquelike accumulations composed of primarily globular neurites. The corpus callosum and subcortical white matter of the cortex show NNs and fibrillar astrocytic tangles. The U-fibers are prominently involved. Subcortical white matter structures such as the extreme and external capsule, anterior and posterior commissures, thalamic fasciculus, and fornix also show NNs and astrocytic tangles.

Dense NFTs, ghost tangles, and astrocytic tangles are found in the olfactory bulbs, hippocampus, entorhinal cortex, and amygdala, often in greater density than is found in AD. Abundant NFTs and astrocytic tangles are also found in the thalamus, hypothalamus, mammillary bodies, nucleus basalis of Meynert, medial geniculate, substantia nigra (pars compacta more than the pars reticulata), locus caeruleus, superior colliculus, periaqueductal gray, medial lemniscus, oculomotor nucleus, trochlear nucleus, ventral tegmental area, dorsal and median raphe, trigeminal motor nucleus, pontine nuclei, hypoglossal nucleus, dorsal motor nucleus of the vagus, inferior olives, and reticular formation. The nucleus accumbens is usually moderately affected; the globus pallidus, caudate, and putamen are less involved. In the brainstem and spinal cord, midline white matter tracts show dense astrocytic tangles especially around small capillaries. Fibrillar astrocytic tangles are also common in the subpial and periventricular zones. Neurons in the spinal cord gray matter contain NFTs, and astrocytic tangles are frequent in the ventral gray matter. This unique

pattern of tau-immunoreactive pathology was found in all 3 of our cases, with increasing severity from Case A to Case C.

Case A

Neurofibrillary tangles immunopositive for tau epitopes (Appendix) were prominent in the inferior frontal, superior frontal, subcallosal, insular, temporal, and inferior parietotemporal cortices (Fig. 1). Primary visual cortex showed no NFTs; anterior and posterior cingulate cortex showed only scant NFTs. Neurofibrillary tangles occurred in irregular patches, often greatest at the sulcal depths (Fig. 2). Tau-positive fibrillar astrocytes (“astrocytic tangles”) were prominent in foci, especially in subpial regions and around small blood vessels (Figs. 2, 3). Neurofibrillary tangles were especially numerous in cortical laminae II and III, where a prominent perivascular distribution of neuronal NFTs and fibrillar astrocytic tangles was evident (Fig. 3). Although some neuronal NFTs showed multiple tau-positive perisomatic processes, most neuronal NFTs were morphologically similar to those found in AD. In the cortex, there were many tau-positive astrocytes bearing a corona of tau-positive processes. These tau-positive protoplasmic astrocytes were similar in appearance to the astrocytic plaques of corticobasal degeneration, except that the perikaryon was often tau positive (Fig. 3).

Neuropil neurites and astrocytic tangles were abundant in the frontal and temporal white matter (Fig. 3). Neuropil neurites were often dotlike and spindle-shaped, in addition to threadlike forms similar to those found in AD. The hippocampus, entorhinal, and transentorhinal cortex contained dense NFTs, ghost tangles, and NNs, including many ghost tangles in CA1 and subiculum; NFTs were denser in the anterior hippocampus compared with the posterior hippocampus. The amygdala showed dense tau immunoreactivity, including NFTs, astrocytic tangles, and NNs (Fig. 4). Neurofibrillary tangles were most frequent in the lateral nuclear group of the amygdala.

The nucleus basalis of Meynert, hypothalamic nuclei, septal nuclei, fornix, and lateral mammillary bodies showed dense NFTs and astrocytic tangles. Neurofibrillary tangles and astrocytic tangles were also found in the olfactory bulb, thalamus, caudate, and putamen. The globus pallidus and



FIGURE 1. Case A. Whole-mount 50- μ m coronal sections immunostained for tau with monoclonal antibody AT8 and counterstained with cresyl violet showing irregular patchy deposition of phosphorylated tau protein in frontal, subcallosal, insular, temporal, and parietal cortices and the medial temporal lobe.

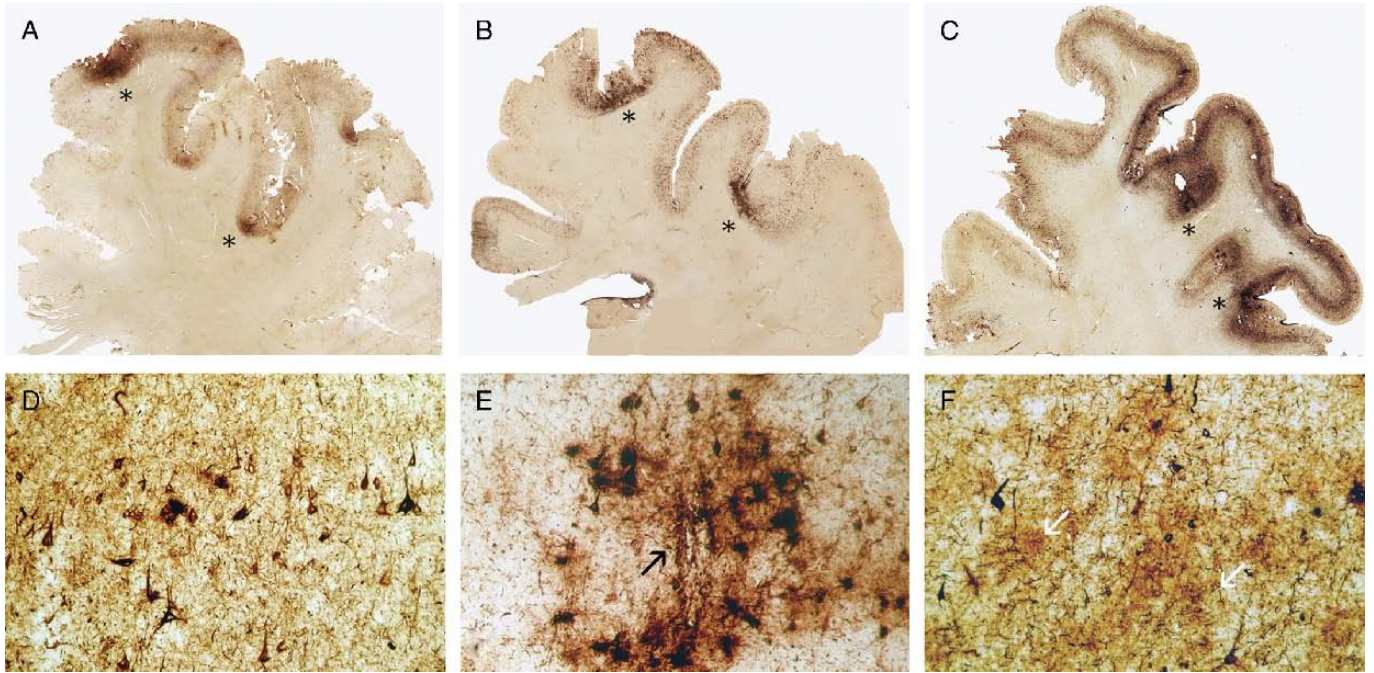


FIGURE 2. (A–C) Whole-mount 50-µm coronal sections of superior frontal cortex from Case A (A), Case B (B), and Case C (C) immunostained for tau with monoclonal antibody CP-13 showing extensive immunoreactivity that is greatest at sulcal depths (asterisks) and is associated with contraction of the cortical ribbon. (D–F) Microscopically, there are dense tau-immunoreactive neurofibrillary tangles (NFTs) and neuropil neurites throughout the cortex, Case A (D), Case B (E), and Case C (F). There are focal nests of NFTs and astrocytic tangles around small blood vessels (E, arrow) and plaquelike clusters of tau-immunoreactive astrocytic processes distributed throughout the cortical layers (F, arrows).

subthalamic nucleus were relatively spared. The lateral substantia nigra pars compacta showed mild neuronal loss, extraneuronal pigment deposition, and moderate numbers of NFTs and NNs. The pars reticulata was unremarkable. The cerebellar peduncle showed mild perivascular hemosiderin deposition. Neurofibrillary tangles were numerous in the dorsal and median raphe nuclei. The internal, external, and extreme capsules, fornix, and mammillothalamic tract showed moderate NNs, although in general, the white matter was less affected than adjacent gray matter.

Case B

There were abundant tau-positive NFTs, glial tangles, and dotlike and spindle-shaped NNs in the superficial layers of cerebral cortex (I–III) (Fig. 3). Cortical tau pathology was most prominent in patchy areas of the superior frontal and temporal lobes, especially the medial temporal lobe, often in a vasocentric pattern. The olfactory bulb, hippocampus, entorhinal cortex, and amygdala showed extremely dense NFTs with many ghost tangles (Figs. 4–6). Tau-positive glia and NNs were also found in the subcortical white matter and corpus callosum. The olfactory bulb, thalamus, hypothalamus, nucleus basalis, striatum, globus pallidus, substantia nigra, raphe, periventricular gray, locus caeruleus, oculomotor nucleus, red nucleus, pontine base, tegmentum, reticular nuclei, inferior olives, and dentate nucleus showed dense NFTs and glial tangles. Spindle-shaped NNs and tau-positive glia were pronounced in the midline white matter tracts of the brainstem.

Case C

Microscopic examination showed dense accumulations of tau-immunoreactive NFTs, astrocytic tangles, and NNs in irregular patches of the dorsolateral frontal, insular, subcallosal, inferior frontal, superior parietal, and posterior temporo-occipital cortices, and most severely in the medial temporal lobe. The hippocampus, entorhinal cortex, and amygdala contained extremely dense NFTs with ghost tangles and severe neuronal loss (Figs. 4, 6). Tau-positive glia and NNs were also found in the subcortical white matter, particularly in the subcortical U fibers. The olfactory bulb, thalamus, hypothalamus, nucleus basalis, striatum, globus pallidus, substantia nigra, raphe, periventricular gray, locus caeruleus, oculomotor nucleus, red nucleus, pontine base, pontine tegmentum, hypoglossal nuclei, reticular nuclei, inferior olives, midline tracts of the medulla, and dentate nucleus contained dense NFTs and astrocytic tangles (Figs. 5, 7). Subcortical white matter tracts including the anterior and posterior commissure, thalamic fasciculus, and external and extreme capsule also showed astrocytic tangles and NNs.

The abnormal tau proteins that are found in the glial and neuronal tangles in CTE are indistinguishable from NFTs in AD and are composed of all 6 brain tau isoforms (39). Neuropathologically, CTE resembles several other neurodegenerative diseases characterized by accumulations of hyperphosphorylated tau protein in neurons or glial cells, including ALS/PDC of Guam, postencephalitic parkinsonism, PSP, corticobasal degeneration, and frontotemporal

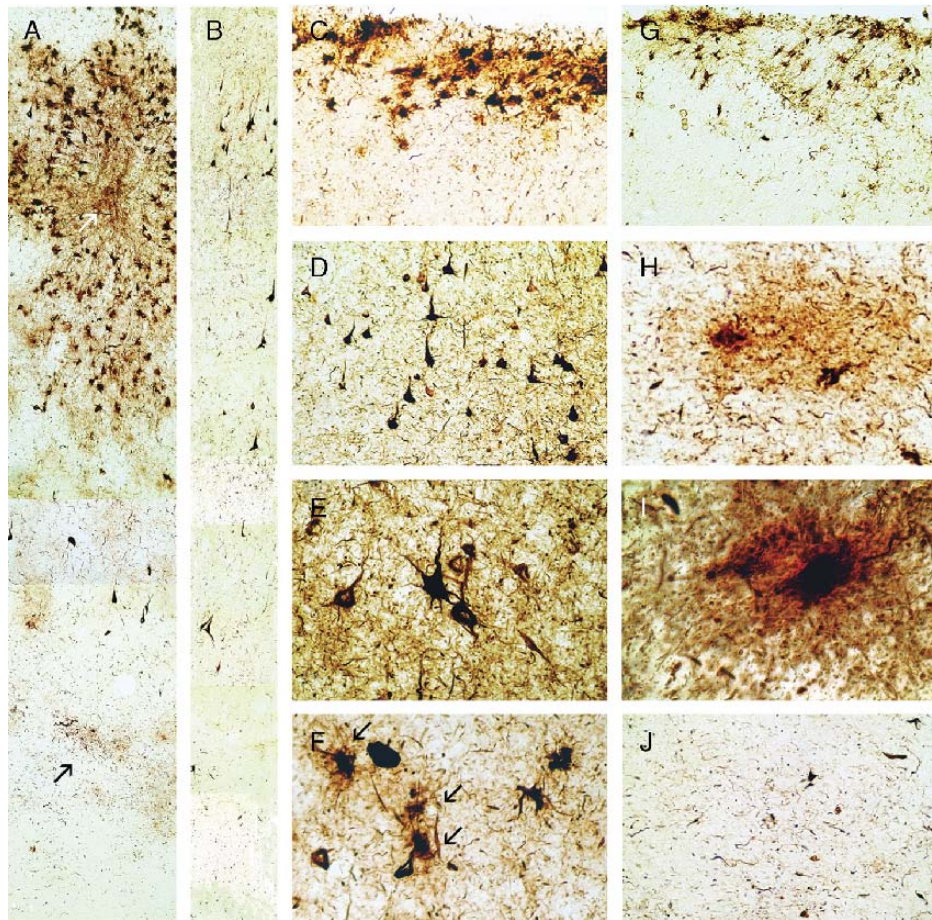


FIGURE 3. Whole-mount 50- μ m sections from Cases A and B immunostained with anti-tau monoclonal antibody AT8. **(A)** Case B. There is a prominent perivascular collection of neurofibrillary tangles (NFTs) and astrocytic tangles evident in the superficial cortical layers with lesser involvement of the deep laminae. Prominent neuropil neurites (NNs) are found in the subcortical U-fibers (arrow). Original magnification: 150 \times . **(B)** Case A. There is a preferential distribution of NFTs in Layer II and NNs extending into the subcortical white matter even in mildly affected cortex. Original magnification: 150 \times . **(C)** Case A. Focal subpial collections of astrocytic tangles and NFTs are characteristic of chronic traumatic encephalopathy (CTE). Original magnification: 150 \times . **(D)** Case A. The shape of most NFTs and NNs in CTE is similar to those found in Alzheimer disease. Original magnification: 150 \times . Some NFTs have multiple perisomatic processes **(E)**, and spindle-shaped and dotlike neurites are found in addition to threadlike forms. **(E)** Case A. Original magnification: 350 \times . **(F)** Case A. Astrocytic tangles are interspersed with NFTs in the cortex (arrows). Original magnification: 350 \times . **(G)** Case A. Tau-immunoreactive astrocytes are common in periventricular regions. Original magnification: 150 \times . **(H, I)** Case A. Tau-immunoreactive astrocytes take various forms; some appear to be protoplasmic astrocytes with short rounded processes **(H, I)** double immunostained section with AT8 (brown) and anti-gliofibrillary acidic protein (red). **(H)** Original magnification: 350 \times . **(I)** Original magnification: 945 \times . **(J)** Case B. Dotlike or spindle-shaped neurites predominate in the white matter, although there are also some threadlike forms. Original magnification: 150 \times .

dementia with parkinsonism linked to chromosome 17 (FTDP-17) (36, 48–50). Similar to ALS/PDC of Guam, neurofibrillary tau pathology in CTE is found in the medial temporal lobe structures, cerebral cortex, and spinal cord, with only a subset of cases showing evidence of diffuse plaques (51). Similar to ALS/PDC and PSP, CTE preferentially involves the superficial cortical layers and involves the accumulation of tau-immunoreactive astrocytes (36). However, CTE differs from ALS/PDC of Guam and PSP in that the cortical involvement is irregular and patchy, greatest at sulcal depths, and distributed in a prominent perivascular, periventricular, and subpial pattern. Furthermore, there is a

unique regional involvement of subcortical and brainstem structures in CTE (Tables 5, 6).

β -Amyloid Deposition

β -Amyloid ($A\beta$) deposition is an inconstant feature in CTE. Fourteen of the 15 brains originally described by Corsellis et al (29) and 6 additional boxers were reexamined by Roberts and colleagues (18) using $A\beta$ immunocytochemistry with formic acid pretreatment; 19 of the 20 cases showed widespread diffuse $A\beta$ deposits. Similarly, Tokuda and colleagues (52) found abundant diffuse $A\beta$ deposits in 8 cases of CTE and cerebrovascular $A\beta$ deposits in 3 cases. In

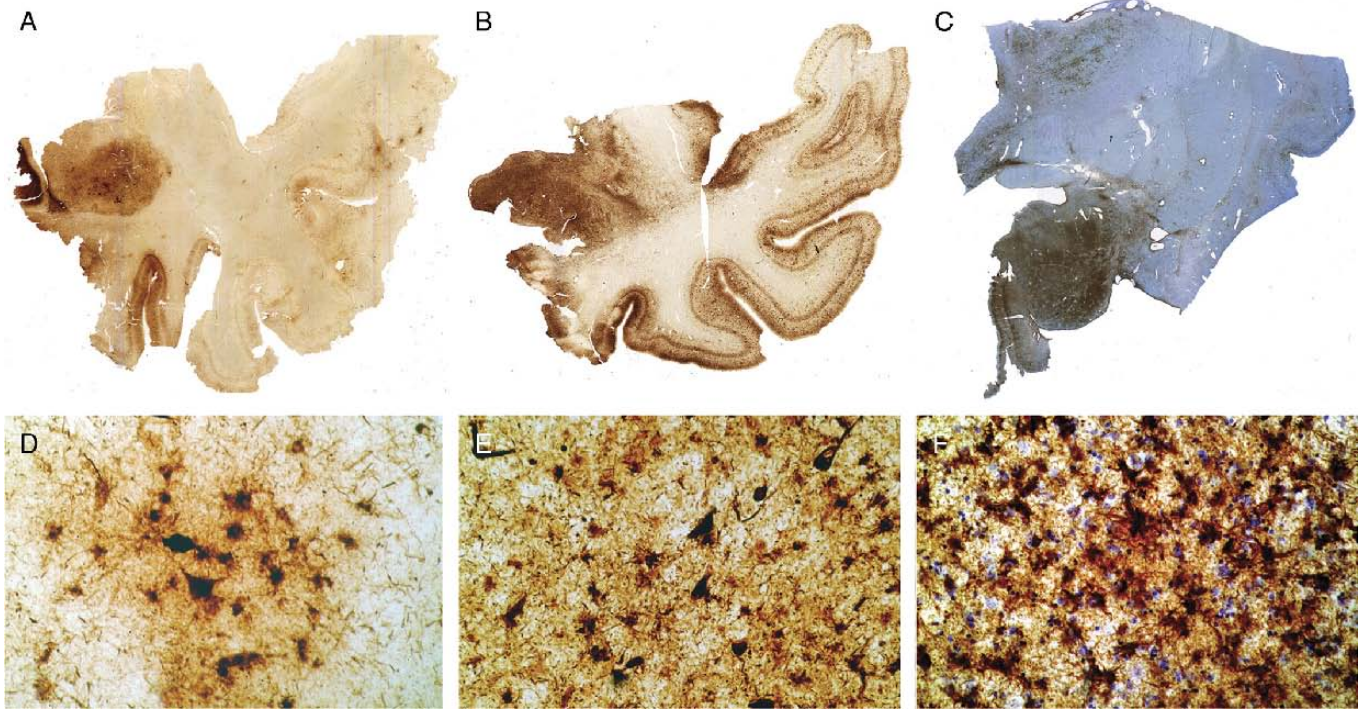


FIGURE 4. (A–C) Whole-mount 50- μ m-thick coronal sections immunostained for tau (AT8) from Case A (A), Case B (B), and Case C (C) counterstained with cresyl violet showing extremely dense deposition of tau protein in the amygdala with increasing severity from left to right. (D–F) Microscopically, there is a moderate density of neurofibrillary tangles and astrocytic tangles in Case A (D), the density is increased in Case B (E), and extremely marked in Case C (F). Original magnification: 350 \times .

our series, only Case B showed moderate numbers of diffuse A β plaques in the frontal, parietal, and temporal cortices, and sparse neuritic plaques; there was no vascular amyloid. Of the 51 neuropathologically verified cases of CTE, diffuse plaques were found in 24 (47%), neuritic plaques in 13 (27%), and amyloid angiopathy in 3 (6%). There was also 1 report of a fatal cerebral hemorrhage from amyloid angiopathy associated with CTE (15).

White Matter Changes and Other Abnormalities

Tau-positive fibrillar astrocytic tangles are found in the white matter, but the major abnormality is that of dotlike or

spindle-shaped tau-positive neurites. The shape of the tau-immunoreactive neurites is distinct from the predominantly threadlike forms found in AD and suggests an axonal origin. Tokuda and colleagues (52) characterized the NNs in CTE as shorter and less prominent than the neuropil threads found in AD and not spatially related to senile plaques. Generally, tau abnormalities in the white matter are not as severe as in adjacent gray matter. Other abnormalities frequently found in the cerebral and cerebellar white matter include small arterioles with thickened fibrohyalinized walls with perivascular hemosiderin-laden macrophages, widened perivascular spaces, and white matter rarefaction. In our Cases A to C,

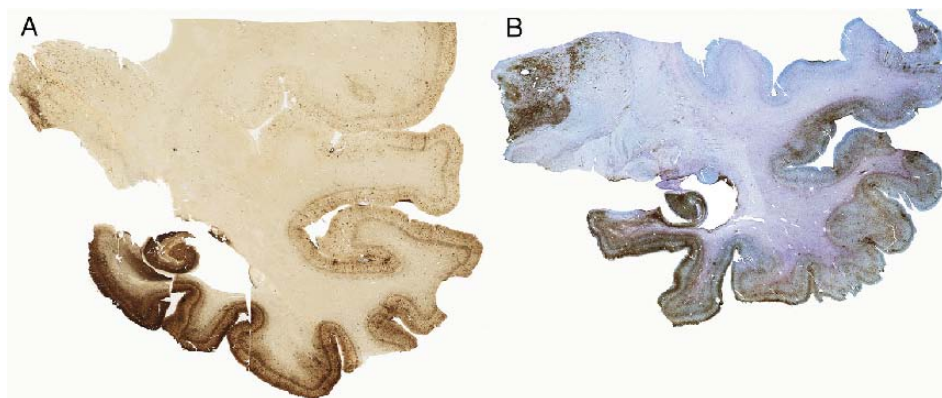


FIGURE 5. Whole-mount 50- μ m coronal sections of Case B (A) and Case C (B) immunostained for tau (AT8) and counterstained with cresyl violet. There is extremely dense deposition of tau protein in the hippocampus and medial temporal lobe structures. There is also prominent tau deposition in the medial thalamus.

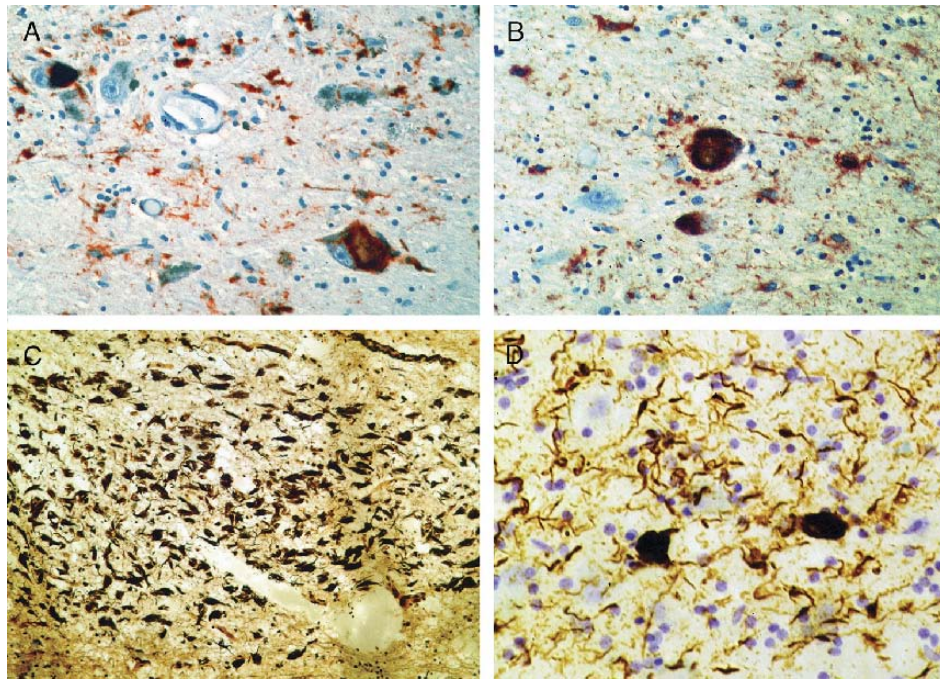


FIGURE 6. Tau-immunoreactive (AT8) neurofibrillary tangles (NFT), astrocytic tangles, and neuropil neurites are found in many subcortical nuclei including the substantia nigra (**[A]** Case C. Original magnification: 350 \times) and nucleus basalis of Meynert (**[B]** Case C. Original magnification: 350 \times). The NFTs are also abundant in the olfactory bulb (**[C]** Case B. Bielschowsky silver method. Original magnification: 150 \times) and thalamus (Case A. Original magnification: 350 \times). The AT8 immunostain counterstained with cresyl violet).

mild to moderate myelin and axonal losses were found in the corpus callosum and subcortical white matter of the frontal and temporal lobes and cerebellum, with mild perivascular hemosiderin deposition.

α -Synuclein Staining

Extensive accumulation of α -synuclein has been found in axons after acute TBI (53), but α -synuclein immunostaining was not a feature of any of the 51 cases of CTE, including our 3 cases.

CLINICOPATHOLOGIC CONSIDERATIONS

The distribution of the tau abnormalities in CTE suggests distinctive core pathology within the amygdalo-hippocampal-septo-hypothalamic-mesencephalic continuum,

that is, the Papez circuit (54, 55). The early involvement of these anatomical regions, sometimes referred to as *emotional* or *visceral* brain, may underlie many of the early behavioral symptoms, including the tendency toward emotional lability, aggression, and violent outbursts. The early involvement of the hippocampus, entorhinal cortex, and medial thalamus may explain episodic memory disturbance as a frequent presenting symptom (56). Neurofibrillary degeneration of the frontal cortex and underlying white matter most likely contributes to the dysexecutive symptoms. Although less common and generally less severe, neurofibrillary degeneration in the dorso-lateral parietal, posterior temporal, and occipital cortices likely accounts for the visuospatial difficulties. The parkinsonian features found in 41.1% of cases are likely caused by degeneration of the substantia nigra pars compacta. The gait



FIGURE 7. Whole-mount tau (AT8)-immunostained 50- μ m coronal sections of the brainstem from Case C showing severe involvement of the locus caeruleus, pontine tegmentum, pontine base, midline medulla, and hypoglossal nuclei.

disorder, variously described as staggered, slowed, shuffled, or frankly ataxic, may result from a combination of cortical and subcortical frontal damage, degeneration of cerebellar tracts in the brainstem, direct cerebellar injury, as well as parkinsonism from substantia nigra pathology. Similarly, speech abnormalities, most often described as slowed and slurred, likely reflect multiregional degeneration. Symptoms of dysarthria, dysphagia, and ocular abnormalities probably result from degeneration of brainstem nuclei, for example, the hypoglossal and oculomotor nuclei.

POSSIBLE MECHANISMS OF CEREBRAL INJURY

Acceleration and deceleration forces are thought to be important events in concussion, particularly rotational acceleration and deceleration (57–59). Sagittal (front-to-back) injuries result in relatively good recovery, whereas lateral (side-to-side) injuries produce the most injury, with injury directed related to the severity of the generating force (58). Conceivably, a concussive impact imparts a fluid wave in the lateral ventricles that produces a shearing force on the septum pellucidum; this may explain the development of an enlarged cavum septum pellucidum and, if severe or repeated, fenestrations.

The patchy irregular location of the cortical NFTs and astrocytic tangles suggests that the distribution is related to direct mechanical injury from blows to the side or top of the head, given their multifocal dorsolateral frontal and parietal, inferior frontal and occipital, and lateral temporal distribution. The possibility that ischemia may contribute to the development of the tau pathology is suggested by the concentration of tau-immunoreactive pathology at the depths of sulci. Damage to the blood-brain barrier and release of local neurotoxins might explain some of the tendency toward perivascular nests of tau-immunoreactive NFT, tau-positive glia, and NNs (13). Buee et al (60) studied the microvasculature of several cases of dementia pugilistica and found decreased microvascular density and tortuosity, with a strong correlation between the laminar distribution of NFTs and pathological microvasculature. Buee and colleagues (60) suggested that the shear forces of repetitive head trauma might lead to vascular damage followed by perivascular NFT and NN formation. Further supporting a possible vascular connection to the pathological changes in CTE, Bouras et al (61) reported that, upon laser microprobe mass analysis, NFTs and nuclei of NFT-free neurons in CTE contained substantially higher amounts of iron and aluminum than NFTs in AD.

Acute TBI

Axonal Injury

Acute concussion produces diffuse axonal injury (62). The “diffuse degeneration of the cerebral white matter” was first described by Strich (63) as the shearing or mechanical tearing of axons at the time of injury. It is now appreciated that axons are not sheared at the time of injury, except in the most severe instances of diffuse axonal injury, but instead undergo a series of changes that may result in a secondary axotomy within 24 hours (64). The axolemma is one of the initial sites of injury; the increased permeability, uncontrolled

influx of Ca^{++} , swelling of mitochondria, disruption of microtubules, and alterations in axonal transport that follow produce axonal swelling and secondary axotomy (64–66). Rapid axonal swelling, perisomatic axotomy, and Wallerian degeneration may also occur without changes in axolemmal permeability, suggesting that trauma may have diverse effects on axons. McKenzie et al (67) showed that 80% of patients who died of acute head injury showed immunocytochemical evidence of axonal injury within 2 hours of injury; after 3 hours of injury, axonal bulbs were identified, and as the survival time increased, the amount of axonal damage and axonal bulb formation increased. Axonal injury was found most frequently in the brainstem, followed by the internal capsule, thalamus, corpus callosum, and parasagittal white matter (67). Axonal damage may continue for weeks after the acute TBI (68).

Deposition of Abnormal Proteins

In individuals undergoing surgical brain tissue resection for acute TBI, tau-immunoreactive dystrophic axons were found in the white matter, and diffuse tau immunoreactivity was found in some neuronal cell bodies, dendrites, and glial cells within 2 to 3 hours postinjury (67). Studies of acute TBI in experimental animal models and postmortem human brain also demonstrate that A β deposition and amyloid precursor protein processing, production, and accumulation are increased after injury (69–78). Increased amyloid precursor protein production in experimental TBI has also been associated with heightened neuronal loss in the hippocampus (73, 79). In acute TBI, diffuse cortical A β plaques have been found in 30% to 38% of cases as early as 2 hours after injury (73, 76, 80). In addition, individuals with cortical A β plaques showed increased levels of soluble A β_{42} , and half were apolipoprotein E (ApoE) $\epsilon 4$ allele carriers (81). In acute TBI, A β deposition is widely distributed throughout the neocortex without apparent association with the injury sites (82). The predominant form of A β in acute TBI is A β_{42} , whereas the A β_{40} form predominates in serum and cerebrospinal fluid, a situation similar to that in AD (83). A recent report also showed that interstitial soluble A β concentrations in the brain seem to directly correlate with neurological outcome after TBI (84).

NEURONAL DEATH IN ACUTE TBI AND RELATIONSHIP TO CTE

There are multiple reasons for neuronal loss in acute traumatic injury including neuronal death from direct physical damage, necrosis from the immediate release of excitatory transmitters such as glutamate, and diffuse delayed cell death involving both necrotic and apoptotic death cascades (85, 86). Other contributing factors include focal ischemia, breakdown of the blood-brain barrier, inflammation, and the release of cytokines. Experimental lateral percussive injury in the rat produces apoptotic and necrotic neuronal death that progresses for up to 1 year after injury, with degeneration of the cortex, hippocampi, thalami, and septum, ventriculomegaly, and impaired memory performance (62, 85, 87–89). The thalamic degeneration typically follows the cortical degeneration by weeks, suggesting that a secondary process

such as deafferentation may play a role in the thalamic neuronal death. Neuronal loss in the hippocampus and thalamus has also been reported after blunt head injury in humans using stereological techniques (90, 91). One of the key features of CTE is that the disease continues to progress decades after the activity that produced traumatic injury has stopped. It is most likely that multiple pathological cascades continue to exert their effects throughout the individual's lifetime once they are triggered by repetitive trauma; the longer the survival after the initial events and the more severe the original injuries, the greater the severity of the neurodegeneration. It is clear that neuronal loss, cerebral atrophy, and ventricular enlargement all increase with longer survival and greater exposure to repetitive trauma.

DIAGNOSIS OF CTE

Presently, there are no available biomarkers for the diagnosis of CTE. Although significant decreases in cerebrospinal fluid ApoE and A β concentrations have been reported that correlated with severity of the injury after TBI, there have been no similar studies in CTE (92). Nonetheless, advances in neuroimaging offer the promise of detecting subtle changes in axonal integrity in acute TBI and CTE. Standard T1- or T2-weighted structural MRI is helpful for quantitating pathology in acute TBI, but diffusion tensor MRI (DTI) is a more sensitive method to assess axonal integrity in vivo (93, 94). In chronic moderate-to-severe TBI, abnormalities on DTI have been reported in the absence of observable lesions on standard structural MRI (83). More severe white matter abnormalities on DTI have been associated with greater cognitive deficits by neuropsychological testing (94, 95), and increases in whole-brain apparent diffusion coefficient and decreases in fractional anisotropy using DTI have been found in boxers compared with controls (96, 97).

GENETIC RISK AND THE ROLE OF APOE4

Apolipoprotein E genotyping has been reported in 10 cases of CTE, including our most recent cases. Five (50%) of the 10 cases of CTE carried at least 1 ApoE ϵ 4 allele, and 1 was homozygous for ApoE ϵ 4 (our Case A). The percentage of ApoE ϵ 4 carriers in the general population is 15%; this suggests that the inheritance of an ApoE ϵ 4 allele might be a risk factor for the development of CTE.

In acute TBI, there is accumulating evidence that the deleterious effects of head trauma are more severe in ApoE ϵ 4-positive individuals (98–100). Acute TBI induces A β deposition in 30% of people (75, 76), and a significant proportion of these individuals are heterozygous for ApoE ϵ 4 (101, 102). Apolipoprotein E4 transgenic mice experience greater mortality from TBI than ApoE ϵ 3 mice (102). Furthermore, transgenic mice that express ApoE ϵ 4 and overexpress amyloid precursor protein show greater A β deposition after experimental TBI (103).

GUIDELINES FOR PREVENTION AND TREATMENT

Clearly, the easiest way to decrease the incidence of CTE is to decrease the number of concussions or mild TBIs.

In athletes, this is accomplished by limiting exposure to trauma, for example, by penalizing intentional hits to the head (as is happening in football and hockey) and adhering to strict "return to play" guidelines. Proper care and management of mild TBI in general and particularly in sports will also reduce CTE. No reliable or specific measures of neurological dysfunction after concussion currently exist, and most recommendations are centered on the resolution of acute symptoms such as headache, confusion, sensitivity to light, and so on (104). Asymptomatic individuals have been shown, however, to have persistent decreases in P300 amplitudes in response to an auditory stimulus at least 5 weeks after a concussion, thereby casting doubt on the validity of the absence of symptoms as a guidepost (105, 106). Neuropsychological tests have also helped provide estimates of the appropriate time for athletes to return to practice and play. Studies using event-related potentials, transcranial magnetic stimulation, balance testing, multitask effects on gait stability, positron emission tomography, and DTI MRI have all shown abnormalities in concussed athletes or nonathletes with TBI lasting for 2 to 4 weeks (105, 107–109). These studies indicate that safe return to play guidelines might require at least 4 to 6 weeks to facilitate more complete recovery and to protect from reinjury, as a second concussion occurs much more frequently in the immediate period after a concussion (106, 110). In addition, experimental evidence in animals suggests that there is expansion of brain injury and inhibition of functional recovery if the animal is subjected to overactivity within the first week (111).

CONCLUSIONS

Chronic traumatic encephalopathy is a progressive neurodegeneration clinically associated with memory disturbances, behavioral and personality changes, parkinsonism, and speech and gait abnormalities. Pathologically, CTE is characterized by cerebral and medial temporal lobe atrophy, ventriculomegaly, enlarged cavum septum pellucidum, and extensive tau-immunoreactive pathology throughout the neocortex, medial temporal lobe, diencephalon, brainstem, and spinal cord. There is overwhelming evidence that the condition is the result of repeated sublethal brain trauma that often occurs well before the development of clinical manifestations. Repetitive closed head injury occurs in a wide variety of contact sports as well as a result of accidents or in the setting of military service. Pathologically, CTE shares some features of AD, notably tau-immunoreactive NFTs, NNs, and in approximately 40% of cases, diffuse senile plaques. Furthermore, the A β and NFTs found in CTE are immunocytochemically identical to those found in AD, suggesting a possible common pathogenesis. Multiple epidemiological studies have shown that head injury is a risk factor for AD, and there have been several case reports citing an association between a single head injury and the development of subsequent AD (112, 113). Just as acquired vascular injury may interact additively or synergistically with AD, traumatic injury may interact additively with AD to produce a mixed pathology with greater clinical impact or synergistically by promoting pathological cascades that result in either AD or CTE. In athletes, by instituting and following proper

guidelines for return to play after a concussion or mild TBI, it is possible that the frequency of sports-related CTE could be dramatically reduced or, perhaps, entirely prevented.

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APPENDIX

Methods for Analysis of Cases A to C

The following anatomical regions were microscopically evaluated in paraffin sections in Cases A to C: olfactory bulb, midbrain at level of red nucleus, right motor cortex, right inferior parietal cortex (Brodmann Area [BA] 39, 40), right anterior cingulate (BA 24), right superior frontal (BA 8, 9), left inferior frontal cortex (BA 10, 11, 12), left lateral frontal (BA 45, 46), caudate, putamen, and accumbens (CAP), anterior temporal (BA 38), superior temporal (BA 20, 21, 22), middle temporal cortex, inferior temporal cortex, amygdala, entorhinal cortex (BA 28), globus pallidus, insula, substantia innominata, right hippocampal formation at the level of the lateral geniculate, hippocampus, thalamus with mammillary body, thalamus, posterior cingulate (BA 23, 31), calcarine cortex (BA 17,18), superior parietal cortex (BA 7B), cerebellar vermis, cerebellum with dentate nucleus, parastriate cortex (BA 19) pons, medulla, and spinal cord.

The sections were stained with Luxol fast blue and hematoxylin and eosin, Bielschowsky silver impregnation, and by immunohistochemistry with antibodies to phosphoserine 202 and phosphothreonine 205 of PHF-tau (mouse monoclonal AT8; Pierce Endogen, Rockford IL; 1:2000), α -synuclein (rabbit polyclonal; Chemicon, Temecula, CA; 1:15,000), A β (mouse monoclonal; Dako North America Inc, Carpinteria, CA; 1:2000) (after formic acid pretreatment), and A β 42 (rabbit polyclonal; Invitrogen [Biosource], Carpinteria, CA; 1:2000). In addition, multiple large coronal fragments were cut at 50 μ m on a sledge microtome and stained as free-floating sections using a mouse monoclonal antibody directed against phosphoserine 202 of tau (CP-13; courtesy of Peter Davies; 1:200); this is considered to be the initial site of tau phosphorylation in NFT formation (114–118). Other monoclonal antibodies used for immunostaining were AT8, phosphoserine 396, and phosphoserine 404 of hyperphosphorylated tau (PHF-1; courtesy of Peter Davies; 1:1000) (114–118), glial fibrillary acidic protein (Chemicon; 1:2000), and HLA-DR-Class II major histocompatibility complex (LN3; Zymed, San Francisco, CA; 1:2000); some of these sections were counterstained with cresyl violet.