Neurodegeration after mild and repetitive traumatic brain injury: chronic traumatic encefalopathy

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Abstract:

Repetitive brain trauma is associated with a progressive neurological deterioration, now termed as chronic traumatic encephalopathy (CTE). Although research on the long-term effects of TBI is advancing quickly, the incidence and prevalence of post-traumatic neurodegeneration and CTE are unknown. The incidence and prevalence of chronic traumatic encephalopathy and the genetic risk factors critical to its development are currently under research. CTE can be diagnosed only by post mortem neuropathological examination of the brain. Great efforts are being made to better understand the clinical signs and symptoms of CTE, obtained in most cases retrospectively from families of affected persons.Patients with CTE are described as having behavioral, mood, cognitive and motor impairments, occurring after a long latency from the traumatic events. Recent pathogenetic studies have provided new insights to CTE mechanisms, offering important clues in understanding neurodegenerative process and relations between physical factors and pathologic protein deposition. Further research is needed to better identify the genetic and environmental risk factors for CTE, as well as rehabilitation and treatment strategies.

Key words: mild traumatic brain injury, traumatic encephalopathy, neurodegeneration, tau aggregates, cognitive impairment

Traumatic brain injury: definitions and epidemiology

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity around the world. TBI is divided into three grades of severity: mild, moderate, and severe, based on the Glasgow Coma Scale, the loss of consciousness, and the development of post-traumatic amnesia.

TBI is a world health problem: each year about 1% of the population in developed countries experiences a clinically relevant TBI (1), resulting in at least 1 million emergency department consultations annually in UK (2), with 90% of them being mild TBI (mTBI). Epidemiological studies mentioned 42 million people worldwide affected by mTBI or concussion every year (5).

Mild TBI definition criteria, after Mayo Traumatic Brain Injury Classification system (3) include one or more of the following signs and symptoms: loss of consciousness momentarily to less than 30 min, post-traumatic anterograde amnesia momentarily to less than 24 h, depressed, basilar or linear skull fracture (dura intact). Possible (symptomatic) TBI criteria are also included if one or more of the following symptoms are present: blurred vision, confusion (mental state changes), daze, dizziness, focal neurologic symptoms, headache, nausea. The diagnosis of mild TBI is challenging, because lack of abnormal findings on conventional CT san or MR imaging.

There is still no universal consensus regarding the definition of "concussion". For some authors, concussion and mild TBI should be viewed as distinct entities, other authors (for example American Academy of

Neurology guidelines 2013 for sports concussion) do not separate them. Proposed definition for "concussion" is "a clinical syndrome of biomechanically induced alterations of brain function, typically affecting memory and orientation, which may involve loss of consciousness" (4).

"Subconcussive" traumatism is defined as biomechanical force to the head similar to or less than that required for the symptomatic concussion but without symptoms and clinical presentation consistent with concussion (10)

Concussive and subconcussive forms of closed-head injury due to impact or blast trauma represent the most common types of TBI in both civilian and military population. Although mild traumatic brain injury, including concussion and subconcussion, is by far the most common, it is also the most difficult to diagnose and the least well understood.

Acute and long-term post-traumatic sequelae after single-TBI.

After a single TBI, well known complications are evident immediately after the event: focal neurologic signs and neurocognitive symptoms, with variable duration, in some cases lasting for months or longer. Permanent brain damage with incomplete recovery and residual motor, sensory and cognitive deficits are the delayed sequelae after a single-incident moderate or severe TBI.

Evidence indicates that a single traumatic brain injury of moderate to severe intensity can precipitate or accelerate multiple age-related neurodegenerations, increase the risk of developing Alzheimer's disease, Parkinson's disease, and motor neuron disease (ALS). (5) (6). The pathological sequence which linked single TBI to neurodegenerative diseases begin with "diffuse axonal injury (DAI)", which alters cell physiological processes (like proteolysis and proteostasis) and lead to accumulation of abnormal protein aggregates into the cells and brain parenchyma. (1).Both idiopathic and post-traumatic neurodegeneration involve accumulation of protein aggregates (tau, amyloid beta, alfa-synuclein, TDP-43, etc), and possibly share common pathogenetic pathways.

Long term consequences after repetitive, mild TBI

In the last decades, medical and lay literature have become aware of cognitive consequences – especially dementia- described after mild and repetitive brain traumatic injuries, like those produced in contact sports or military personnel. It is also becoming increasingly clear that mild traumatic brain injuries have persistent, and sometimes progressive, long-term debilitating effects. This consequences of TBI have received media attention following reports of progressive neurological dysfunction in known athletes, football players or military veterans.

Neurologic and psychiatric changes were observed since early 1900s in people suffering from mild or moderate TBI. In 1928, Martland described "punch drunk" syndrome in professional boxers. This condition was later referred as "dementia pugilistica" by Millspaugh in 1937. First neuropathologic description of neurodegeneration after minor TBI appears in 1927, by Osnato and Gilberti, but specific neuropathologic features of post-traumatic neurodegeneration were described by Corsellis in 1973 (7).

Neurologic, behavioral and cognitive specific features were then described in the literature, and this condition is now termed "chronic traumatic encephalopathy (CTE), term used by Critchley for the first time in 1949.

Chronic traumatic encephalopathy (CTE)

CTE is a progressive and unique neurodegenerative disease that develops as a result of repetitive mild traumatic brain injury

(8). In most cases, the clinical symptoms of the disease begin after a long period of latency after the traumatic factors exposure (several years or even decades). CTE is a neurodegenerative disease characterized by the accumulation of pathologic protein aggregates (hyperphosphorilated tau protein) in neurons and astrocytes (10). CTE is considered to be a "tauopathy".

The exact **incidence and prevalence** of CTE are not known, the condition can only be diagnosed by post mortem neuropathological examination of the brain. Great efforts are being made to better understand the clinical signs and symptoms of CTE, obtained in most cases retrospectively from families of affected persons.

Etiology: Most instances of CTE occur in association with the play of sports, but CTE has also been reported in association with blast injuries and other neurotrauma. The groups of individuals at risk for CTE because of repetitive head traumatisms are: contact sport athletes (boxers, American football players, soccer or rugby players, wrestlers, martial arts practicants), epileptics with poor control of seizures, military personnel (especially after blast injuries), domestic abuse victims, disabled individuals with head-banging behavior (9), (10).

Given the large population that could be potentially affected, CTE is an important public health problem. Every year, in the US, between 1,6 and 3,8 million individuals experience a sport-related concussion, especially young people (in high school and college) (10).

Incidence of CTE in specific sport categories is 3,7% lifetime prevalence in American football players, but reach 20% in retired professional boxers (11).

Relationship between mild and repetitive head traumatisms and neurodegenerative process is quite clear: all cases of neuropathologically confirmed CTE have had a history of repetitive head impacts (10). Mild repetitive TBIs are necessary to cause to cause the beginning of pathogenetic mechanism, the history of head impacts is not sufficient to cause CTE. Not all individuals with repetitive head traumatisms develop neurodegeneration and CTE, proving the role of additional risk factors (genetic or physical) in producing CTS, factors which remain largely unknown.

Risk factors for developing CTE are mechanical, depending on the characteristics of impact exposure: age at first exposure, frequency, impact force. Genetic risk factors also play a role: apolipoprotein (ApoE) ε4 allele and polymorphism of neprilysin were associated with negative outcome after TBI (9). Environmental factors like lifestyle comorbidities in contact sport athletes and military veterans also play a role, recreational drug use, alcohol abuse, opioid consumption, stress or performance-enhancing drugs being incriminated in CTE production (1), (9).

Clinical presentation. Clinical symptoms appear long period of time after the head impacts: years or decades after exposure to trauma are needed for the CTE to develop. CTE presents clinically with symptoms classified into four domains: mood, behavior, cognition and motor.

1.Mood features include most frequently depression, irritability and hopelessness, but also anxiety, fearfulness, high rate of suicidal ideas, labile emotions, insomnia, apathy, flat affect, loss of interest or fatigue.

2.Behavioral symptoms include: impulsivity, explosivity, loss of control, aggression, rage, short fuse, physical or verbal violence, desinhibited speech or behavior, childish behavior, personality changes, paranoid ideas, psychosis.

3.Cognitive features can include memory loss, executive dysfunction, dementia in advanced stages, but also impaired attention and concentration, visuospatial difficulties or language troubles.

4.Motor signs are: parkinsonism, ataxia, dysartria, gait troubles, tremor or spasticity.

All these clinical signs begin insidiously and most often progress slowly over decades, in 68% of the cases a progressive evolution was described (10).

Cases of CTE described earlier tended to report more motor signs, as parkinsonism, dysarthria and ataxia and were predominantly boxers, with different impact characteristics which involve mainly midbrain structures ; these cases were grouped as "classical CTE". "Modern CTE" cases described mainly American football players with predominantly mood and cognitive features.

Stern and colleagues described two distinct clinical forms of CTE: an "early type" which begin with mood and behavioral changes in young adults (around 35 years), and progress toward cognitive impairment later, and a second clinical presentation, with a later age of onset (6-th decade), with predominantly cognitive impairment.

Current research effort are focused on the definition of clinical diagnostic criteria. Montenigro and al suggested a new terminology of clinical symptoms associated with repetitive brain trauma: they called the typical association of symptoms "traumatic encephalopathy syndrome", and reserve the name "CTE" for Cases with same symptomatology but with anatomopathologic confirmation (10).

General criteria for diagnosis of traumatic encephalopathy syndrome after Montenigro and colleagues are (10):

- History of multiple impacts to the head
- No other neurological disorder that could explain the clinical features
- Clinical features should be present for a minimum of 12 months.
- At least one of the core clinical features (cognitive impairments, behavioral disorders and mood changes) must be present and should be interpreted as a decline from baseline functioning
- At least two supportive features must be present (impulsivity, anxiety, apathy, paranoia, suicidality, headache, motor signs, documented decline and delayed onset)

CTE classification includes 3 groups (10):

1. Probable CTE: meets criteria for traumatic encephalopathy syndrome stated above, have progressive course and has a minimum of one potential biomarker for CTE
2. Possible CTE: meets classification criteria for traumatic encephalopathy syndrome, has progressive course, but no biomarker
3. Unlikely CTE: does not meet traumatic encephalopathy syndrome criteria

Neuropathologic characteristics. Like many other neurodegenerative diseases, CTE is diagnosed with certainty only by neuropathological examination of brain tissue. CTE presents a neuropathological profile resembling those observed in chronic neurodegenerative disorders, like Alzhemier disease (AD) and Parkinson disease, but with specific features.

Macroscopic examination of the brain in individuals with CTE shows lobar cortical atrophy, involving the frontal and temporal lobes in early stages, with mild enlargement of the frontal horns of the lateral ventricules or third ventricle and with septal abnormalities (cavum septum pellucidum), but also with pallor of substantia nigra and locus coeruleus. Advanced cases shows severe atrophy of medial temporal lobes or global atrophy, atrophy of thalamus and hypothalamus, generalized atrophy of the white matter (7), (9), (11).

Microscopically, a severe spongiosis of layer 2 of the cerebral cortex, neuronal loss, astrocytosis and myelin loss in the white matter. Abnormal deposits of hyperphosphorylated tau (τ) as neurofibrillary tangles and disordered neuritis were described throughout the brain.

CTE was included in the group of tauopathies, characterized by the deposition of hyperphosphorylated tau (p-tau) protein as neurofibrillary tangles, astrocytic tangles and neuritis. The deposition begins around small blood vessels of the cortex, typically at the sulcal depths. In later stages, p-tau pathology extends widespread throughout the brain, particularly dense in medial temporal lobes. The process begins focally then graduately spreads to other regions of the brain, mainly the frontal and temporal lobes, medial temporal lobe, diencephalon and brainstem (7).

CTE is distinguished from other neurodegenerative disorders by the distinctive topographic (perivascular and in sulcal depths, with subpial and periventricular involvment) and cellular pattern of tau neurofibrillary pathology (neurofibrillary tangles NFTs, neuropil threads and glial tangles).

CTE have been recently associated with accumulation of another phosphorylated protein aggregate, TDP-43 (43 kDa TAR DNA-binding protein) in medial temporal lobe and brainstem initially, and frontal lobe in later stages. TDP-43 is an RNA-binding protein that regulates RNA metabolism. After brain injuries, TDP-43 relocates from the nucleus and accumulates into the neuronal cytoplasm. TDP-43 role could be mediation of response to injury of the neuronal cytoskeleton. Abnormalities in phosphorylated 43 kDa TAR DNA-binding protein are found in most cases of CTE.

There are rare beta amyloid 1-42 (Aβ1-42) plaques in CTE in most cases, but in older patients, beta-amyloid is identified in 43%, associated with age.

The mild brain impacts damage also brain vessels and the blood-brain-barrier (BBB), which will lead to microhemorrhages and inflammation into the white and gray matter (7).

Axonal damage is another pathological element observed in CTE. In early stages, distorted axons with varicosities are found in the cortex, subcortical white matter and deep white matter tracts of diencephalon, and in later stages frontal and temporal lobes have the most severe changes.

Globaly, CTE presents with accumulation of hyperphosphorylated tau neurofibrillary and glial tangles, dystrophic neurites, 43 kDa TAR DNA-binding protein (TDP-43) neuronal and glial aggregates, microvasculopathy, myelinated axonopathy, neuroinflammation, and white matter degeneration.

Pathogenetic mechanism. Mild traumatisms produce axonal injury, with changes in axolemma permeability, massive influx of calcium and release of caspases and calpains that produce the misfolding, truncation, phosphorilation and aggregation of proteins, including tau and TDP-43. Accumulation in time of misfolded tau proteins, caused by repetitive injuries, might overwhelm the normal cell capacity to clear these pathologic proteins.

Some studies suggest that phosphorylated tau may stimulate the deposition of other abnormal protein aggregates, such as Aβ amyliod, TDP-43 and alpha-synuclein.

Association with other neurodegenerative diseases. Chronic traumatic encephalopathy frequently occurs as a sole diagnosis, but may be associated with other neurodegenerative disorders, including Alzheimer's disease, Lewy body disease, and motor neuron disease. Both idiopathic and post-traumatic neurodegeneration involve accumulation of protein aggregates, but with different disposition.

Studies suggest that cranio-cerebral traumatisms are risk factors for dementia, most frequently of Alzheimer type. A large number of CTE patients have also alpha-synuclein aggregates under the form of Lewy bodies in the brainstem or amygdala. CTE is also considered to be a form of acquired tauopathy.

The idiopathic tauopathy is called fronto-temporal lobe degeneration (FTLD) and is characterized by accumulation of tau-protein aggregations in frontal and temporal lobes. Is important to mention that TDP-43 protein aggregates were found in spinal anterior horn neurons, in patients with amyotrophic lateral sclerosis (ALS).

In vivo diagnosis. Actually, CTE can only be diagnosed by postmortem anatomopathological examination of the brain, although there are many ongoing research studies examining biomarkers and neuroimagistic innovative techniques that might have diagnostic utility. There are no objective and validated biomarkers of CTE.

Neuroimagistic techniques: A major concern for clinicians is detection of small changes in brain structure and function caused by the traumatisms. Actually there are new imaging modalities, which can identify concequences of mild TBI (11): diffusion tensor imaging (DTI) detects axonal injury, functional MRI is able to detect deficits after concussion or subconcussion, SWI techniques can detect microhemorrhages, MR spectroscopy is also of great value in assessing subtle changes. Both conventional and new MRI techniques can detect subtle changes, which can be considered as potential biomarkers for probable CTE. These structural abnormalities are: cavum septum pellucidum, cortical thinning on measurement, cortical atrophy.

Positron emission tomography (PET) with ligands specific for Aβ or tau is of great value. Studies have suggested that negative amyloid PET imaging (excludes Alzheimer disease) in the presence of positive tau imaging (confirms tauopathy) could be a valuable biomarker.

Biomarkers can be obtained from body fluids: blood or cerebrospinal fluid (CSF).

Plasma biomarkers are easier to obtain, but are less specific. Serum levels of the glial protein S-100B are elevated after TBI, but non specific. Neuron specific enolase (NSE) remains elevated long time after TBI. Measurement of tau protein in serum with a new ELISA technique (digital ELISA) can detect small amounts of tau protein, and could be a promising biomarker.

CSF biomarkers are obtained by invasive methods, but CSF is in dorect contact with the brain, and reflects biochemical changes at that level. Studies have shown increased levels of CSF neurofilament light polypeptide. Other studies reported elevated tau levels in the CSF, and elevated p-tau/tau ratio in the presence of normal beta amyloid CSF levels. Studies have also shiw that GFAP (gliofibrillary acid protein) levels were increased in the CSF.

Treatment strategies: The best methods are prevention of the initial traumatism, using different methods: public education in identifying minor traumatisms, changement of game rules in sports, in order to stop the game if mild traumas appear, and adequate management of minor TBIs. Given the importance of sports participation and physical exercise to physical and psychological health as well as disease resilience, it is critical to identify the genetic risk factors for CTE as well as to understand how other variables, such as stress, age at exposure, gender, substance abuse and other exposures, contribute to the development of CTE.

Future directions for research. Knowledge gaps include elucidation of pathogenic mechanisms, identification of genetic risk factors, and clarification of relevant variables-including age at exposure to trauma, history of prior and subsequent head trauma, substance use, gender, stress, and comorbidities-all of which may contribute to risk profiles and the development of post-traumatic neurodegeneration and CTE. Researchers made promising efforts to develop imaging, spinal fluid, and peripheral blood

biomarkers to diagnose and monitor the course of disease in living subjects.

Conclusion. Chronic traumatic encephalopathy CTE is an emerging public health problem, disease prevalence being greater than expected (increasing popularity of contact sports and extension of military conflict zones). CTE is a disabling condition, with an devastating deterioration of cognitive function and loss of autonomy. Precise clinical criteria are needed for diagnosis, and the search for biomarkers is ongoing. We need a more complete understanding of the real incidence, prevalence and risk factors for this condition, in order to apply efficient therapeutic strategies.

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