

Recurrent Head Trauma: A Trigger of the Alzheimer Cascade or the Cause of an Independent Pathologic Entity? - An Explicative Case of Chronic Traumatic Encephalopathy Mimicking Alzheimer's Disease

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Abstract

Repeated traumatic brain injuries have a negative impact on brain integrity and cognition. It was hypothesized that they could trigger the AD amyloidogenic cascade or they could represent a peculiar clinical entity labelled as "chronic traumatic encephalopathy", CTE. To contribute in the understanding of this controversy we describe the case of a boxer with early onset dementia, reporting biomarkers and neuropsychological assessment with the effort to differentiate the AD diagnosis and CTE. We discuss, for each element, its possible role with regard to the opposite diagnostic directions and we highlight, on the example of our probable CTE patient, the necessity of better defined diagnostic criteria for the chronic traumatic encephalopathy.

Keywords: Traumatic brain injuries; Chronic traumatic encephalopathy; Alzheimer's disease; Dementia

Introduction

It is universally accepted that repeated traumatic brain injuries (TBI) have a negative impact on brain integrity and cognition and, recently, growing attention has been focused on the cognitive decline in contact sports, including boxing [1].

Unfortunately, the exact link between TBI and cognitive impairment is still unclear. On one hand it was hypothesized that TBI could trigger the amyloidogenic cascade leading to the formation of amyloid plaques typical of Alzheimer Disease (AD) [2] and might represent a risk factor for the subsequent development of AD [3]. On the other hand, it has been suggested that the cognitive decline associated with TBI could represent a clinical entity itself independent from AD, for which several research diagnostic criteria have been proposed [4-6]. Overall, the studies in literature refer to this clinical picture as "chronic traumatic encephalopathy", CTE. An amount of evidences seem to confirm TBI as the trigger event for a progressive neuronal damage that may be accelerated by the accumulation of repeated TBIs. CTE is the long term consequence of repeated TBIs, also of mild intensity, as frequent in contact sports as boxe, hockey, martial arts and American Football [7]. It is a chronic neurodegeneration that follows recurrent TBIs and it is characterised by cognitive and psycho behavioural symptoms that appear after a long or very long latency, in the large part of cases years after the traumatic events, with an observed latency that ranges from few weeks to some decades [8].

A proposed pathway hypothesize that multiple TBIs induce a diffuse axonal injury with an alteration of the axonal transport, with consequent functional and trophic events, including a progressive axonal disconnection and wallerian degeneration [9]. These initial events seem to induce immunotoxicity with a switch of microglia toward a neuro-destructive phenotype and consequent accumulation of phosphorylated tau protein an amyloid beta protein that are considered typical of the CTE [10] but also of the AD brain. At now, the diagnosis of CTE is still autptic.

To contribute in the understanding of this controversy, we describe the case of a professional boxer with early onset dementia, reporting

biomarkers and neuropsychological assessment with the tentative of differentiate AD diagnosis and CTE.

Case Report

The patient, a 52 years old man, formerly professional boxer with a 16 years long career in featherweight division, came to our memory clinic in "Luigi Sacco" Hospital of Milan. His wife reported the insidious appearance of forgetfulness and complaints in daily life. Then, a progressive spatial disorientation, even in known routes, was observed. To note, affective disorders (apathy, emotional flattening and poor insight) were one of the dominant features of the clinical picture. His family history was unremarkable for any neurological disease, including cognitive decline. At the time of medical examination, neither significant illness nor current treatments were reported in patient's history. During his career, he reported many TBI and he suffered one knockout.

The patient was evaluated with general clinical and neurological examination, neuropsychological testing, blood test, brain Magnetic Resonance Imaging (MRI), electroencephalography, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and underwent lumbar puncture for Cerebrospinal Fluid (CSF) Amyloid (A) β_{1-42} , tau and Phospho (P)tau evaluation.

Neurological examination demonstrated mild cerebellar dysfunction with slight inaccuracy in the coordination tests. Blood tests

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were unremarkable. The neuropsychological profile (Table 1) showed multi domain deficits, including episodic memory impairment, frontal lobe dysfunction, constructional apraxia, language deficits. The Mini Mental State Examination (MMSE) score was 20/30 and the functional scale shown the first stage of a compromised self-sufficiency. Brain MRI displayed a severe cortical and sub-cortical atrophy, with few vascular brain lesions (Supplementary Figure 1A). The FDG-PET showed a diffuse cortical hypometabolism (Supplementary Figure 1B). CSF examination was normal on the chemical and physical aspects: Absence

of cells; protein 323 mg/dL (normal values, n.v.: 150-450 mg/L); glucose 58 mg/dL (n.v. 40-70 mg/dL), with glycaemia 87 mg/dL. The profile of CSF A β_{1-42} and tau proteins was not suggestive for AD (545 and 267 pg/mL, respectively) according to the formula described by Duits et al. [7] (Tau/A β_{42} >0.52). pTAU value was instead slightly elevated (63 pg/mL; n.v.:<61). The apolipoprotein E (APOE) genotype was 3/3.

At a 33 month clinical follow-up a global severe deterioration in cognitive function was observed: MMSE was excessively complex to be administrable and self-sufficiency was totally compromised (ADL: 2/6; IADL: 0/6). His wife reported occasional episodes of verbal and physical aggressiveness, for which the patient takes low dose of quetiapine.

Discussion

We report the clinical history, the biomarkers findings and the neuropsychological results of a case of rapidly progressive dementia occurring in a former professional boxer. The CSF results report normal value of CSF A β_{1-42} protein, confirming the possibility that the cognitive decline associated with TBI could be triggered by a pathogenic mechanism different from the amyloidogenic cascade [8].

It is a controversial issue, whether the cognitive impairment in recurrent TBI represents a specific clinical entity, directly induced by TBI [9] or if it is simply AD [3], precipitated by TBI, in subjects predisposed to develop AD.

In the reported case, some clinical and biological markers are both for and against the CTE diagnosis, even if it seems to be the most realistic one.

In fact, even if the clinical phenotype, the neuropsychological profile [10,11] and the FDG-PET results [12] could evoke AD, the same neuropsychological profile and the FDG-PET findings denote a damage of brain cortex that may result not only from the AD process, but also from repeated TBI. It has been suggested [4] a link between repetitive TBI and the damage of frontal and temporal lobes, which are supposed to be areas of least resistance. It has been hypothesized [13] that trauma produces disproportionate white matter loss associated with consequently hippocampal atrophy. From a clinical standpoint, this results in a complex syndrome very similarly to AD.

Moreover, many aspects of the present case argue against the hypothesis of AD. First, the negative family history, together with a 3/3 APOE genotype, suggest a low genetic susceptibility profile for AD. Second, based on the results of the CSF, it seems unlikely that the pathogenesis of this case of dementia can be related to the amyloidogenic cascade typical of AD. During the AD process, both the reduction of A β_{1-42} protein and the increase of T-tau and P-tau have been described [14]. CSF T-tau and A β_{1-42} were shown to optimally discriminate AD from other dementias in an autopsy-confirmed study [14]. On the contrary, amyloid beta deposition is not a pathologic feature of CTE [4], with the possibility to have normal beta amyloid value even in cases with severe cognitive decline (as in the case described here) [8]. Recent neuropathological studies of TBI cases have described amyloid plaques acutely after a single severe TBI and tau pathology after repeat TBI. This has helped drive the hypothesis that a single moderate to severe TBI increases the risk of developing late onset AD, while repeat TBI increases the risk of developing CTE [15].

At the light of all these investigations, this patient seems to have not AD, but more probably CTE. The absence of a family history of AD, the presence of cerebellar signs, the ApoE3 genotype, the negativity of CSF A β_{1-42} , drive the diagnostic process toward a diagnosis of CTE. Furthermore, also MRI and FDG-PET findings seem not to support

	Range	r.s.	c.s.	cut-off	e.s.
Global Cognition					
Mini-mental state ^a	0+30	20	19.97	24	
- temporal orientation	0+5	4			
- spatial orientation	0+5	5			
Raven Coloured Progressive Matrices 47 ^b	0+36	11	11.5	18.96	0
Long-Term Memory					
Rey Auditory Verbal Learning Test ^b	0+75	14	13.8	28.53	0
- delayed recall	0+15	1	0.9	4.69	0
- recognition (hits)	0+15	8			
- recognition (false alarms)	0+30	9			
Story recall ^c	0+28	0+4	3.5	8	0
Language					
Token Test ^e	0-36	19	18.1	≥ 26,5	0
Category Fluency ^f	0+∞	24	25.7	25	1
Letter Fluency ^b	0+∞	21	22.7	17.35	2
Constructional Praxis					
Clock Drawing Test ^g	1+10	3		6	
Complex Ray Figure Copy ^d	0+36	§		28.88	
Executive Functions					
Frontal assessment battery ^h	0+18	11	11	13.5	0
Trail making test – A ⁱ	0+180	>180		<93	0
Trail making test – B ⁱ	0+300	*		<282	
Clinical Dementia Rating Scale^e	0+5	1		<1	

r.s.: Raw Score; c.s.: Corrected Score; e.s.: Equivalent Score
 §: Presence of closing-in behavior
 *: The trial run wasn't understood by the patient
^a Measso G, Cavarzeran F, Zappalà G (1993) The mini-mental state examination: Normative study of an Italian random sample. *Dev Neuropsychol* 9: 77-95.
^b Carlesimo GA, Caltagirone C, Gainotti G (1996) The mental deterioration battery: Normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. *Eur Neurol* 36: 378-384.
^c Novelli G, Papagno C, Capitani E (1986) Tre test clinici di memoria verbale a lungo termine. Taratura su soggetti normali (normative values of three tests of verbal long-term memory). *Archivio di Psicologia Neurologia e Psichiatria* 47.
^d Caffarra P, Vezzadini G, Dieci F (2002) Rey-Osterrieth complex figure: Normative values in an Italian population sample. *Neurol Sci* 22: 443-447.
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ⁱ Giovagnoli, AR, Del Pesce M, Mascheroni S (1996) Trail making test: Normative values from 287 normal adult controls. *Ital J Neurol Sci* 17: 305-309.
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Table 1: The neuropsychological examination showed multi domain deficits including long-term memory impairment, executive dysfunction, language deficits and constructional apraxia.

the diagnosis of AD: Cortex of hippocampus, post cingulate gyrus and precuneus, most commonly affected by AD, are rather preserved on MRI that, on the contrary, shows subcortical atrophy and leucodystrophy, typical response to multiple years brain injuries. With regard to FDG-PET, such drastic hyporeactivity of glucose metabolism, when found in AD, generally reflect a very low MMSE score, less than 10 and not 20 as in our patient. Also these MRI and PET evidences reinforce the diagnosis of CTE.

The mechanism by which acute TBI may lead to the neurodegenerative process of CTE associated with tau hyperphosphorylation remains speculative [16]: Focal tau-positive neurofibrillary tangles in close proximity to axonal injury and the CTE-tau pathology may result in an inflammatory cascade with microglia and astrocyte activation [17]. Recently two cases of dementia after moderate-severe traumatic brain injury were described and authors showed the variety of misfolded proteins that may accumulate after TBI: Neuropathological findings revealed in both patients abundant β -amyloid neuritic and cored plaques, diffuse β -amyloid plaques and frequent hyperphosphorylated-tau neurofibrillary tangles involving much of the cortex. In one case they also found white matter rarefaction while in the other patient diffuse cortical Lewy bodies were present.

From a clinical and diagnostic standpoint, a huge heterogeneity in the definition of the CTE does exist. There are no standardized and univocally intended diagnostic criteria and the CTE construct itself is heterogeneous. In Table 2, we report the main diagnostic criteria for CTE and similar; Jordan's diagnostic criteria [4] defined CTE mainly depending on the neuropathological confirmation. From a clinical point of view, the Author identifies a cognitive and/or behavioural impairment with cerebellar dysfunction and pyramidal tract or extrapyramidal diseases. In contrast to Jordan's criteria, the diagnostic criteria of Victoroff [5] are focused on a broad of clinical signs and symptoms. The Victoroff's criteria represent an important addition to

the literature, but require the "persistence of both symptoms and signs for at least two years after the traumatic exposure"; this is not consistent with numerous cases of CTE for which a delayed onset is often observed [18]. Recently, Montenegro and colleagues proposed research criteria for the "traumatic encephalopathy syndrome (TES)" [6]. The Authors have detailed the clinical presentation of the CTE, differentiating the general criteria from the core and supportive features.

The existence of a dementia induced or anticipated by TBI may offer an interesting and useful model in neurodegeneration studies and consequently these patients have to be extensively investigated including detailed MRI studies, PET scan, CSF biomarkers and markers of epigenetic modifications. It has been recently observed [19] that brain plasticity is largely influenced by the dynamic modulation of gene expression primarily linked to DNA methylation, posttranslational modifications of histones and noncoding RNAs that facilitate or suppress gene expression: Through these mechanisms, the brain plastically responds to experiences and maybe also to TBI. Elements that may accelerate the methylation process seem to be able to accelerate the progressive brain ageing and TBI might be one of these elements.

The last decade has seen an increased interest in understanding the relationship between TBI and the development of neurodegenerative disorders; the topic has garnered considerable attention from the media as CTE is closely linked to participation in sports such as American football and to head injuries sustained by soldiers participating in the conflicts.

Therefore, it would be mandatory to reduce the existing heterogeneity of CTE construct standardizing the diagnostic criteria and identifying a clinical entity itself of dementia related to TBI.

From a public health standpoint, it would allow to have a window of observation of the clinical trajectory of the phenomenon in order to implement preventive strategies for subjects at risk. Just as an example,

Jordan [4]	Victoroff [5]	Montenegro et al. [6]
<p>Definite CTE: Any neurological process consistent with the clinical presentation of CTE along with pathological confirmation.</p>	<p>A. History of probable or definite exposure to one or more head injuries, traumatic brain injuries, concussions or subconcussive brain injuries, with or without known loss of consciousness.</p> <p>B. Onset of persistent or progressive neurological or neurobehavioral symptoms post-dating the traumatic exposure.</p> <p>C. Presence of objective neurological or behavioural signs.</p> <p>D. Persistence of both symptoms and signs for at least two years after traumatic exposure.</p> <p>E. No alternative diagnosis. Probable TE: A, D, E as well as at least two symptoms and three signs. Possible TE: A, D, E and one symptom and two signs.</p>	<p>General criteria: 1. History of multiple impacts to the head. 2. No other neurological disorder that likely accounts for all clinical features. 3. Clinical features must be present for a minimum of 12 months. 4. At least one core clinical features must be present and should be considered a change from baseline functioning. 5. At least two supportive features must be present.</p>
<p>Probable CTE: Two or more of the following conditions: Cognitive and/or behavioural impairment; cerebellar dysfunction; pyramidal tract diseases or extrapyramidal diseases; clinically indistinguishable from any known disease process and consistent with the clinical description of CTE</p>		<p>Core clinical features (at least one): 1. Cognitive: Difficulties in cognition. 2. Behavioural: Emotionally explosive, physically and/or verbally violent. 3. Mood: Feeling overly sad, depressed and/or hopeless.</p>
<p>Possible CTE: Any neurological process that is consistent with the clinical description of CTE but can be potentially explained by other known neurological disorders</p>		<p>Supportive features (a minimum of two of the following): 1. Impulsivity. 2. Anxiety. 3. Apathy. 4. Paranoia. 5. Suicidality. 6. Headache. 7. Motor signs. 8. Documented decline. 9. Delayed onset.</p>
<p>Improbable CTE: Any neurological process that is inconsistent with the clinical description of CTE and can be explained by a pathophysiological process unrelated to brain trauma</p>		

Table 2: Different diagnostic criteria for CTE.

in the last few years, observational and epidemiological reports on CTE among certain groups of athletes such as football players were so relevant that in 2013 the National Football League modified some rules of play to reduce the frequency and intensity of TBIs and consequently to protect the health of its athletes. Even, new experimental helmets will be soon tested in the football NCAA championship (National Collegiate Athletic Association) to reduce the consequences of TBIs.

In conclusion, we hope that our case, in synergy with previous similar cases, may reinforce the necessity to improve the knowledge on CTE pathogenesis to better understand also primary neurodegeneration and, by the other hand, that easy diagnostic paradigms and clinical exams will be individuated to allow a widespread follow-up of athletes' espoused to recurrent TBIs to prevent CTE development.

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