TRAUMATIC BRAIN INJURY AND DEMENTIA (K WANG, SECTION EDITOR)

Traumatic Brain Injury: Risk Factors and Biomarkers of Alzheimer's Disease and Chronic Traumatic Encephalopathy

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Abstract A complex interaction between genetic and environmental risk factors has often been a suspected trigger for the development of neurodegenerative disease. Yet of all the possible environmental risk factors, trauma to the central nervous system is one of the most consistent candidates for initiating the molecular cascades that result in several neurodegenerative diseases including Alzheimer's disease (AD). In almost all of the studies investigating traumatic brain injury and AD risk, AD was diagnosed based on clinical criteria for probable or possible AD, without neuropathological verification. Recent evidence also suggests that mild traumatic brain injury, including repetitive concussions and subconcussive trauma, can provoke another distinctive neurodegeneration termed chronic traumatic encephalopathy. Because most reports were based on clinical diagnostic criteria that may lack the specificity to rule out other causes of dementia, it is possible that the increased incidence of dementia following head injuries is due to CTE, alone or in conjunction with other neurodegenerative conditions such as AD. The search for, and validation of, biomarkers for specific neurodegenerative diseases provide disease diagnosis and indicators of risk and disease progression, and offer a means to monitor therapeutic efficacy.

Keywords Traumatic brain injury · Alzheimer's disease · Chronic traumatic encephalopathy · Risk factors · Amyloid beta · Tau · Biomarkers · Neurodegenerative disease

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Introduction

Risk Factors

Alzheimer's disease (AD) is projected to grow substantially in prevalence during the coming decades, with the number of affected individuals expected to reach approximately 8 million by 2030. This figure represents a more than a 50 % increase from current prevalence rates [1]. Research on the risk factors for AD is compelling (Table 1). Age is the primary risk factor for AD. During the course of normal aging, the brain undergoes a number of changes:

(i) Some neurons and the fibers that connect them to other neurons shrink and degenerate, especially neurons in areas of the brain important to learning, memory, planning, and other complex mental activities;

(ii) Tangles develop within neurons and protein plaques develop in the areas surrounding neurons;

(iii) Mitochondria become more susceptible to damage;

(iv) Inflammation increases, such as after a head injury, which can injure nerve cells; and

(v) Oxidative stress increases, leading to nerve cell damage and death.

Genetically, AD is heterogeneous and complex, with age of onset being one of the most evident differences between forms of the disease. Familial (ie, early-onset) AD (FAD) is inherited in a Mendelian manner, but rare, mutations having been described in the three genes that code for amyloid precursor protein, presenilin 1, and presenilin 2 [2]. FAD accounts for less than 1 % of the AD cases. Other than differences in age at onset and inheritance pattern, FAD is clinically similar to the more common late-onset sporadic form of the disease. Although there is no evidence that autosomal dominant inheritance of mutated genes causes

Table 1 Risk factors

Alzheimer's disease

- Age
- Sex
- Family history and genetics (*ApoE*)
- Head trauma
- Prior mild cognitive impairment
- Lifestyle (lack of exercise, smoking, high blood pressure, high cholesterol, poorly controlled diabetes)
- Social engagement (lack of: [i] higher levels of formal education, [ii] mentally challenging activities, [iii] frequent social interactions)

Chronic traumatic encephalopathy

- Head trauma (single or repetitive)
- History of head concussion
- Participation in contact sports (boxing, football, soccer, professional wrestling, hockey)
- Military service (direct contact and blast injuries)
- Epileptics
- Genetics (*ApoE*)

ApoE apolipoprotein E

late-onset AD, genetics does appear to play a role in its development. Currently, the most reliable gene associated with AD is apolipoprotein E (*ApoE*). Carrying the ApoE4 allele lowers overall age at onset for AD [2], though the ApoE genotype does not by itself have any specific implications for the individual carrier. ApoE4 increases the risk of developing AD, but it does not cause the disease. The finding that increased risk for late-onset AD is linked with inheritance of the ApoE4 allele has helped explain some of the variations in age of onset of AD based on whether people have inherited zero, one, or two copies of the ApoE4 allele. Further, although the association between the ApoE4 allele and AD is well accepted, the risk of AD for carriers of the E4 allele is far from 100 %.

More women than men have AD but this is likely because women generally live longer than men; the incidence by age is similar among men and women. Education is also generally agreed upon as a probable risk factor for AD where the risk of AD varies inversely with the level of formal education. The use of certain groups of drugs, including NSAIDs and cholesterol-lowering drugs called statins, also may impact AD risk. Evidence indicates that other lifestyle factors, such as one's dietary habits, high blood pressure, and high cholesterol, may impact one's risk for developing AD.

Evidence implicates traumatic brain injury (TBI) as a risk factor for developing neurodegenerative disorders, such as AD and Parkinson's disease that can become more prevalent with age. There are many pathological features common to both brain injury and AD, including β-amyloid (Aβ) deposition, tau phosphorylation, neurite degeneration, synapse loss, and microgliosis [3, 4]. Neuroinflammatory responses, such as glial

activation leading to amyloid precursor protein upregulation and Aβ deposition, may serve to mediate neuronal injury in both chronic neurodegenerative diseases and brain injury.

More than 3 million Americans (civilians and military personnel) currently have a long-term or lifelong need for help in performing daily activities as a result of a TBI. Recent evidence also suggests that mild TBI, including repetitive concussions and subconcussive (mild) trauma among athletes engaged in contact sports (such as boxers and football and hockey players) and military personnel can provoke a distinctive neurodegeneration known as chronic traumatic encephalopathy (CTE) [5••, 6] (Table 1). CTE is also commonly associated with psychological problems like depression, agitation, aggression and violence, loss of inhibitions, sexual compulsiveness, euphoria, drug and alcohol abuse, and suicide.

Genetic factors also have been thought to play a role in the development of CTE specifically the *ApoE* gene. As discussed above, the ApoE4 allele has been well described in its association with AD, where individuals with homozygous ApoE4 genotype have an increased risk (about 19-fold) of developing AD [7]. This same gene is now thought to possibly have a role in the development of CTE [5••]. Studies have shown that ApoE4-positive individuals had poorer outcomes with head trauma. Teasdale et al. [8] reported that patients with ApoE4 allele are more than twice as likely as those without ApoE4 to have unfavorable outcomes 6 months after head injury. Jordan et al. [9] looked at ApoE4 genotype in boxers in relation to chronic TBI and concluded that ApoE4 may be associated with increased severity of chronic neurologic deficits in high-exposure boxers.

Unfortunately, brain injuries sustained by military personnel as a result of exposure to the force of an explosion without a direct strike to the head, which is one of the most common perils for soldiers in Iraq and Afghanistan, may be underdiagnosed due to the lack of identifiable critically defined clinical parameters, inadequate animal models, and insufficient research on nonpenetrating neurotrauma. A soldier's ability to rebound from a concussion due to a blast event is degraded when he or she is exposed to multiple improvised explosive device blasts in a short timeline. The short-term picture is that soldiers are unable to perform multiple tasks or complex tasks due to their inability to concentrate. The long-term picture for military personnel is that severe, moderate, and/or multiple exposures to significant nonpenetrating neurotrauma can increase the likelihood of seizures and cognitive decline leading to neurodegenerative disorders, in particular CTE and/or AD.

Neuropathology

The classical neuropathological hallmarks of AD are interneuronal plaques consisting of precipitates or aggregates of

various forms of the Aβ protein, and intra-neuronal neurofibrillary tangles (NFTs) of tau protein. However, the concept that soluble oligomers (small soluble aggregates) of amyloid proteins are the acutely toxic structures of these proteins, and not insoluble aggregates like plaques and tangles, is now accepted for multiple neurodegenerative diseases [10, 11].

Pathologically, CTE is a tauopathy characterized by an extensive accumulation of tau-associated NFTs, neuropil threads, and glial tangles. Widespread neurodegeneration and functional deficits result from the accumulation of modified tau (phosphorylated, truncated, hyperphosphorylated, aggregated, polymerized) in neuronal cell bodies presumably leading to alterations in axonal membrane permeability, release of caspases and calpains, and the breakdown of the cytoskeleton with dissolution of microtubules and neurofilaments. However, defining and dissecting the biochemical pathways responsible for these events has not been done and is necessary for realizing treatment options. CTE-induced sublethal, repetitive mild closed head injury occurs before the development of the clinical manifestations, which include memory disturbances, behavioral and personality change, Parkinsonism, and speech and gait abnormalities. Individuals who suffer moderate or repeated mild TBI face an increased risk for developing both short- and long-term health problems later in life. CTE continues to progress decades after the activity that produces TBI has stopped. Although neuropathologically distinct with a younger age of onset and a slower disease course, the clinical presentation of CTE is similar to AD or frontotemporal lobar degeneration (FLD) [5••]. These similarities bring into question the specificity of the clinical diagnostic criteria for AD used in studies that have established TBI as a risk factor for AD. Currently, neuropathologic examination of brain tissue is the only way to diagnose CTE, although intense research efforts are underway to identify biomarkers to detect the disease and monitor its progression and to develop therapies to slow or reverse its course.

Presently, studies into CTE are sparse and there is an absence of clinically accepted criteria for its early detection and differential diagnosis to distinguish it from other neurodegenerative disorders. Clinical parameters and criteria currently used for TBI and dementia (neurological examination, neuropsychological testing) will likely be equally useful when evaluating suspected CTE. To further complicate the CTE field, currently there are no reliable CTE animal models to study risk factors, disease progression or diagnosis, and biochemical events associated with neuropathogenesis. The use of head injury models to provoke neurodegeneration in genetically modified animals will serve to identify and dissect key components of the pathogenetic molecular cascades and potential therapeutic targets. The ability to distinguish AD from CTE has important therapeutic implications and avoids misguided treatments for these conditions. Longitudinal research efforts are underway to shed additional light on the specific variables related to head trauma, neuropathology, and clinical presentation of CTE that remain in question.

Biomarkers

The development and analysis of biomarkers is not only informative in disease diagnosis, but also serves as an indicator of disease risk and rate of disease progression. A short list of the various classes of AD biomarkers includes (i) positron emission tomography (PET) neuroimaging protein deposition; (ii) magnetic resonance imaging (MRI) of brain structures; (iii) genotyping analysis (ie, ApoE); (iv) quantitation of proteins in the cerebrospinal fluid (CSF); and (v) quantitation of proteins in blood.

Currently, no definitive diagnostic test for AD and CTE exists and confirmatory disease diagnosis is only possible by brain biopsy or postmortem examination of brain tissue pathology [12, 13]. In view of this, one cannot overemphasize the importance of biomarkers that not only identify, but also distinguish, AD and CTE. Three AD biomarkers extensively reported in the literature are Aβ protein 1-42 (Aβ1-42), total tau protein, and phosphorylated tau protein, which are the major components of brain extracellular insoluble senile plaque and NFTs, respectively [13]. As described later in this article, blood and CSF biomarkers have yielded promising results for the detection of AD. Because AD and CTE are similar neuropathologically (although there are differences in the cortical distribution of NFTs between the two diseases), some of the biomarkers that are used for AD also may be useful for CTE. For instance, CSF tau and phosphorylated tau, and isoprostanes in plasma and CSF, may have the potential to contribute to the prediction and diagnosis of CTE. The determination of this will involve future research efforts.

Although the etiology of AD is not fully understood, the Aβ cascade hypothesis has been the most common view of the pathological pathway of AD. It holds that the generation of Aβ and accumulation of Aβ aggregates in the brain initiate the disease process. It is supported by genetic evidence that mutations leading to increased accumulation of Aβ aggregates leads to familial AD. However, Aβ is not a sufficient target for AD therapeutic development because there are a number of weaknesses in the Aβ cascade hypothesis and it does not address the importance of other pathways that can cause neurodegeneration [14]. The poor correlation between AD and the accumulation of neuritic plaques composed of Aβ has been used to challenge the amyloid hypothesis [15]. In spite of this controversy, the deposition of β-amyloid protein within cortical regions of

the brain is still widely accepted as a pathologic hallmark of AD that is believed to precede clinical symptoms by several years.

The primary function of tau protein is to facilitate assembly and maintenance of microtubules in neuronal axons. In the disease process tau protein becomes modified, loses its affinity to microtubules, and accumulates in the cell body, where it forms aggregates. The large NFTs formed from tau protein assembled into filaments were thought to be the pathological structure of tau. However, more recent work indicates that smaller, soluble, oligomeric forms of tau are best associated with neuron loss and memory impairment. Tau protein has a causative role in neurodegenerative disorders exhibiting tau histopathology collectively termed tauopathies. Tauopathies are a class of neurodegenerative diseases associated with the pathological aggregation of tau protein in the human brain. AD, and more recently CTE, belong to this class in which tau protein is deposited within neurons in the form of NFTs. Tangles are formed by tau hyperphosphorylation causing it to aggregate in an insoluble form. These aggregations of hyperphosphorylated tau protein are also referred to as PHF, or paired helical filaments. The precise mechanism of tangle formation is not completely understood, and it is still controversial whether tangles are a primary causative factor in the disease or play a more peripheral role. However, regardless of the role of tau in disease neuropathogenesis, its use as a biomarker is not disputed.

The concentrations of several proteins in CSF have been associated with increased risk for AD. Among these proteins are Aβ1-42, total tau protein, and phosphorylated tau protein [16–21, 22•]. In the case of Aβ1-42, the correlation between protein concentration and AD is negative in that increased risk for disease is associated with a lower concentration of Aβ1-42 in CSF [18–20]. Although it has been suggested that decreased CSF Aβ1-42 is brought about by sequestration of the protein inside amyloid plaques located throughout the cortex, Lewczuk et al. [23] reported decreased Aβ1-42 concentrations in CSF of patients with Creutzfeldt-Jakob disease where plaques were not present. This points to other mechanisms, such as disturbances in amyloid peptides formation and breakdown in AD. Moreover, CSF Aβ1-42 levels were the lowest in patients with AD who had severe dementia and the longest duration of the disease. The results suggest that CSF Aβ1-42 levels may be associated with the progression of the disease.

The opposite is true for the relationships between AD and tau proteins, which are positively correlated with risk [21]. Elevated levels of total tau and phosphorylated tau in CSF are associated with increased risk of disease. In addition, although decreased CSF β-amyloid protein 1-42 levels are typically observed in patients several years before clinical symptoms and cognitive decline, increased concentrations of total and phosphorylated tau in CSF occur later in the course of disease and are more closely aligned with the onset of disease symptoms. Some evidence suggests that CSF levels of total and phosphorylated tau protein, as well as ratios of Aβ1-42 to other β-amyloid isomers (eg, Aβ1-38 and/or Aβ1-40) and to tau protein, can be used to discriminate between AD and other forms of dementia (eg, vascular or FLD and CTE). In particular, CSF levels of tau proteins that are phosphorylated at serine 181 or threonine 231 have been shown to improve the diagnostic ability of total tau to differentiate between AD and other forms of dementia [24–26]. A recent study of amateur boxers [27•] reported that repetitive mild head trauma induced acute changes in CSF neurofilament light protein, glial fibrillary acidic protein, total tau, and S-100B, even without memory loss or clinical symptoms of a concussion or TBI. These changes suggest central nervous system damage. Although these acute changes normalized after rest, a risk for cumulative injury is possible in the absence of a recovery period.

Biomarkers that have diagnostic and prognostic value in the early stages of AD are of particular interest and importance. In vivo imaging of Aβ in the brain is of particular interest for the identification of individuals at risk for, and in the early stages of, AD. However, a number of recent studies have documented high proportions of cognitively normal individuals with amyloid accumulation on the order of levels observed in patients with AD [28, 29]. MRI is a widely available and relatively inexpensive technique for visualizing detailed internal brain structures and volumes. Hippocampal volume loss is predictive of AD, with an accuracy rate of about 80 %. However, currently accepted methods for measuring volume changes in the hippocampus are labor- and time-intensive. Whole brain atrophy has been reported as a common feature of CTE at autopsy and may be detected with MRI.

Although modern PET ligands have been developed for AD, these ligands have been developed to selectively bind to Aβ or nonselectively to both Aβ and tau. Because Aβ is relatively sparse in CTE brains [5••], ligands that selectively bind to tau are likely to be more useful for CTE [30].

Some researchers have suggested that blood-based screeners should be the first step in the diagnostic process for AD, to be followed by neuroimaging of the brain or CSF protein assessments. However, this approach remains out of reach for clinical use because of the lack of an accurate blood-based assessment device. Although great advancements have occurred in the brain and CSF biomarkers for AD, less momentum has occurred in the area of blood-based biomarkers. In 2007, Ray and colleagues [31] assessed a large number of plasma proteins in an effort to identify a profile of multiple biomarkers that was indicative of AD. These efforts yielded a panel of 18 proteins that were effective at distinguishing patients with AD from control

individuals. The overall classification accuracy for the resulting algorithm was 90 %. The algorithm also accurately identified 81 % of patients who had myocardial infarction (MCI) that progressed to AD within a 2-to-6–year follow-up period [31]. In 2010, O'Bryant and colleagues [32] constructed an algorithm using differences in serum protein concentrations derived from a large group of individuals, including patients diagnosed as having AD and cognitively normal individuals. The authors analyzed 121 proteins related to inflammation, cytoskeletal remodeling, and cell signaling, as well as growth factors, hormones, and other proteins in combination with age, sex, years of education, and ApoE genotype. The analysis generated an algorithm that was highly accurate at identifying cognitive status. The model had an overall diagnostic sensitivity and specificity of 94 % and 84 %, respectively, and an overall accuracy of 95 % for detecting AD [32]. However, the ability of O'Bryant et al. [32] to predict AD or disease progression rates among patients was not reported. A caveat to all blood-based biomarker studies reported to date is that none of the studies have been cross-validated with independent samples of subjects, nor have the blood-based biomarker studies been tested to determine their ability to distinguish AD from other forms of dementia.

Recent advances in research in AD have highlighted the importance of tau in pathogenesis and its use as a target for the development of disease-modifying therapeutics. Evidence from mouse models indicates that tau reduction reverses disease phenotypes [33–35] and is necessary for the development of cognitive deficits in AD models caused by overexpression of Aβ [36]. The pathological, neurotoxic structures of tau most closely associated with AD progression are soluble tau oligomers in mouse models and also accumulate in human disease [37–39].

NFTs have been implicated in mediating neurodegeneration in AD and tauopathies as they correlate well with cognitive deficits and neuron loss [15, 40–43]. However, the study of animal models of tauopathy has shown that memory impairment and neuron loss is dissociated from accumulation of NFT. Strong support for this came from the analysis of transgenic mice that express tau P301L. Expression of tau P301L caused memory impairment, neuron loss, and NFT. However, suppression of expression caused improvement in memory and reduction in neuron loss even as NFTs continued to accumulate clearly demonstrating that pre-tangle tau species were responsible for the neurodegenerative phenotype [33]. The triple transgenic AD mouse model accumulating both tau and Aβ pathology was used to study the effects of immuno-reduction of tau and Aβ. Antibodies against both proteins were needed to improve learning and memory behavior in these mice. Soluble tau, but not NFT, was reduced by the treatment, again showing the dissociation between the neurodegenerative

phenotype and insoluble tau aggregates [34]. Taken together it appears that pre-fibrillar/oligomeric hyperphosphorylated tau plays a key role in neurodegeneration and behavioral impairments [44]. The ability to measure hyperphosphorylated tau oligomers as a biomarker leads the way to developing a theranostic approach to evaluate tauopathies.

Conclusions

TBI results in cognitive impairment and accelerates the neuropathological features of neurodegenerative diseases through the activation of neuroinflammatory mechanisms. Unfortunately, there are no unambiguous in vivo tools or biomarkers to both diagnose and differentiate AD and CTE. Adding to this conundrum is that a definitive diagnosis of CTE is made only following postmortem examination. Identification of differentiating biomarkers would provide key data to clinicians caring for these patient populations, aid in conducting epidemiological studies, and provide objective diagnostic data to support clinical trials and to explore therapies for the disease processes.

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