Traumatic brain injury associates with an earlier onset in sporadic frontotemporal dementia

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Abstract

Background: Currently, there are few studies considering possible modifiable risk factors of frontotemporal dementia (FTD)

Objective: In this retrospective case-control study, we evaluated whether a history of traumatic brain injury (TBI) associates with a diagnosis of FTD or modulates the clinical phenotype or onset age in FTD patients.

Methods: We compared the prevalence of prior TBI between individuals with FTD (N=218) and age and sex-matched AD patients (N=214) or healthy controls (HC; N=100). Based on the patient records, an individual was categorized to the TBI+ group if they were reported to have suffered from TBI during lifetime. The possible associations of TBI with age of onset and disease duration were also evaluated in the whole FTD patient group or separately in the sporadic and genetic FTD groups.

Results: The prevalence of previous TBI was the highest in the FTD group (19.3 %) when compared to the AD group (13.1 %, p=0.050) or HC group (12 %, p=0.108, not significant). Preceding TBI was more often associated with the sporadic FTD cases than the *C9orf72* repeat expansion-carrying FTD cases (p=0.003). Furthermore, comparison of the TBI+ and TBI- FTD groups indicated that previous TBI was associated with an earlier onset age in the FTD patients (B=3.066, p=0.010).

Conclusion: A preceding TBI associates especially with sporadic FTD and with earlier onset of symptoms. The results of this study suggest that TBI may be a triggering factor for the neurodegenerative processes in FTD. However, understanding the precise underlying mechanisms still needs further studies.

Keywords

Frontotemporal dementia, comorbidity, traumatic brain injury, head trauma, risk factors, dementia

INTRODUCTION

Frontotemporal dementia (FTD) is a major cause for early onset dementia in individuals under 65 years [1]. It is an umbrella term for clinically and neuropathologically heterogenous group of neurodegenerative disorders causing frontal and temporal atrophy [2]. The most common clinical subtype of FTD is behavioral variant frontotemporal dementia (bvFTD), characterized by marked changes in behavior, personality, and executive functions [3]. The other main clinical subtypes are non-fluent variant of primary progressive aphasia (nfvPPA) and semantic variant of primary progressive aphasia (svPPA). Any of these FTD subtypes can also be accompanied by motor neuron disease (FTD-MND) [2]. Due to clinical and neuropathological overlap, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are also regarded as part of the FTD spectrum [4]–[6]. The exact pathophysiological mechanisms of different subtypes of FTD are still unknown, but neuropathological studies have discovered that certain protein inclusions are typical for FTD brains. Of these, inclusions containing hyperphosphorylated tau protein or TAR DNA-binding protein 43 (TDP-43) are the most common. Interestingly, tau-positive inclusions are also detected in the brain affected by chronic traumatic encephalopathy (CTE) [7], [8]. However, clinical presentation of the disease appears to be more dependent on the brain area undergoing degeneration rather than the type of proteinopathy [9].

Genetic factors contributing to FTD are relatively well known and several causative mutations have been identified. Over 40 % of FTD cases are familial. The most common causative mutations are the hexanucleotide repeat expansion in the *C9orf72* gene or mutations in the progranulin (*PGRN)* gene, which lead to TDP-43 pathology, as well as mutations in the microtubule-associated protein tau (*MAPT)* leading to tau pathology [10], [11]. Despite the significance of these autosomal dominant mutations, the majority of the FTD cases are sporadic with an unknown etiology. In contrast to other dementias, environmental risk factors associating with FTD have been less studied. Prior epidemiological studies have investigated non-genetic risk factors for FTD, for example education,

immunological disorders, and cardiovascular risk factors and comorbidities [12]–[15]. A few studies have specifically evaluated the risk for developing FTD in individuals with previous traumatic brain injury (TBI) and these suggest an association between FTD and prior TBI [13], [14], [16], [17]. Moreover, previous TBI has been associated with a lower age of onset, regardless of the type of dementia [18]. However, these studies have evaluated the association between TBI and FTD in general but have not included genetic or neuropathological information.

Here, we aimed to evaluate whether a history of preceding TBI associates with sporadic or genetic FTD diagnosis and whether TBI modulates the clinical phenotype or age at onset in the spectrum of genetic and sporadic FTD.

MATERIALS AND METHODS

STUDY PARTICIPANTS

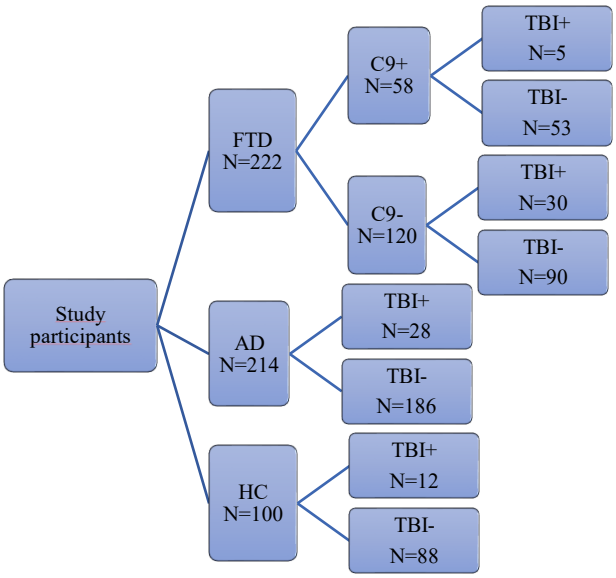
Altogether 218 FTD patients participated in the study, of which 141 patients were diagnosed to have bvFTD, 44 nfvPPA, 9 svPPA, 23 FTD-MND, and 1 PSP in Kuopio and Oulu University hospitals. As a neurodegenerative reference group, 214 age- and sex-matched AD patients were recruited. All the patients were diagnosed by an experienced neurologist specialized in memory disorders using the latest diagnostic criteria for bvFTD, nfvPPA, svPPA, PSP, CBD, or AD [3]–[5], [19], [20]. All the patients underwent a battery of examinations, including neurological examination, routine screening laboratory tests, a neuropsychological examination, and magnetic resonance imaging (MRI) or computed tomography (CT) of the brain. When needed, cerebrospinal fluid analyses of AD biomarkers (β-amyloid$_{42}$, phosphorylated tau, and tau protein) or functional neuroimaging by fluorodeoxyglucose positron emission tomography (FDG-PET) were performed to confirm the diagnosis. Most of the FTD patients underwent genetic testing after giving an informed consent.

Patients were included into the study if they fulfilled at least probable criteria for bvFTD, nfvPPA, svPPA, PSP, CDB, or AD [3]–[5], [19], [20].

The *C9orf72* repeat expansion carriers and FTD patients with Goldman score between 1-3 were categorized into familial FTD group (n=113). FTD patients with Goldman score 4 were classified into sporadic FTD group (n=105) [21]. Goldman score 1 means an autosomal dominant family history of FTD, MND, CBD, or PSP, defined as the presence of at least three affected people in two generations with one person being a first-degree relative of the other two. Goldman score 2 means familial aggregation of three or more family members with dementia but not meeting criteria for 1, Goldman score 3 means one other affected family member with dementia, and 4 is no or unknown family history.

Cognitively healthy controls (HC) group included 100 age- and sex-matched participants. These individuals underwent the uniform evaluations for cognitive disorders (including memory nurse's semi-structured interview for the patients and their caregivers about prior head traumas) similarly to the AD group and were tested to have normal cognition. Individuals in the cognitively healthy control group were allowed to have only mild subjective memory complaints and they showed no signs of progression in the follow-up. Characteristics of the cohorts, and comparisons between FTD, AD, and healthy control groups are described in Table 1. The distribution of the study participants is described in Figure 1 below.

Fig. 1: Distribution of the study participants



Abbreviations: AD = Alzheimer's disease; C9 = *C9orf72* mutation; FTD = frontotemporal dementia; HC = healthy control participant; N = number of cases; TBI = traumatic brain injury

GENETIC ANALYSES

A total of 80,2 % of the FTD patients (n=178) underwent genetic testing for *C9orf72* repeat expansion and of these, 58 (32,6 %) were identified as *C9orf72* repeat expansion carriers. All the patients were of Finnish ancestry. The *C9orf72* repeat expansion status was analyzed from the FTD cohort using the repeat-primed polymerase chain reaction (RP-PCR) [22]. Other mutations, such as *GRN*, *MAPT* and *CHMP2B* mutations are extremely rare in Finnish population, and thus were not systematically screened [23]–[25]. No pathogenic *GRN*, *MAPT* or *CHMP2B* mutations were found in three previous studies within the Finnish FTD patients [25][24] [23]. FTD patients whose *C9orf72* repeat expansion status had not been confirmed using RP-PCR were included only in the analyses encompassing the whole FTD group.

CLINICAL REVIEW

We retrospectively inspected the life-course electronic medical records of all the patients and controls for the history of previous TBI. Each patient and control subject underwent the same diagnostic process, in which a memory nurse interviewed the patient and their caregiver before the visit at the neurologist. The memory nurse interview includes a question on whether the patient had a history of head trauma, and thus the question was asked systematically. These data were combined with other available medical history data from the electronic patient records. Based on the patient records, an individual was categorized to the TBI+ group if they were reported to have suffered from TBI that was associated with alterations in consciousness, loss of memory, or other obvious clinical signs of brain injury (headache, blurred or double vision, vertigo or nausea) during their lifetime. TBI was considered as a possible risk factor if it preceded the symptom onset of dementia.

STATISTICAL ANALYSES

Statistical analyses were performed with SPSS Statistics version 27. Comparison between two categorical variables were compared with binary logistic regression, adjusted for age and sex. The comparison of two continuous variables or continuous and categorical variables were executed with general linear model with similar adjustments. A p-value of ≤ 0.05 was considered statistically significant. Participants with missing data (e.g., patients with unconfirmed *C9orf72* repeat expansion status) were only included in the analyses at the whole group level, not in the subgroup analyses.

RESULTS

We observed that the prevalence of previous TBI was the highest in the total FTD group (19.3 %, n=42) compared to the AD group (13.1 %, n=28) or healthy controls (12 %, n=12). The difference

between FTD and AD patients was statistically significant (p=0.050), whereas the difference between FTD patients and healthy controls was not (p=0.108). Interestingly, preceding TBI especially associated with FTD not linked to the *C9orf72* repeat expansion (n=120) when compared to the *C9orf72* repeat expansion-carrying FTD cases (n=58) (p=0.003). Furthermore, previous TBI associated with an earlier age at onset in the FTD patients (B=3.066, p=0.010). The mean age at onset was 62.1 years in the group of FTD patients without a history of TBI, whereas it was 55.2 years in the group of FTD patients who had suffered from previous TBI. Prior TBI was not associated with disease duration (from diagnosis to death) in FTD patients (B = -0.802, p = 0.395).

Comparing bvFTD TBI+ and non-bvFTD TBI+ groups and bvFTD TBI+ and HC TBI+ groups separately, no statistically significant differences were found in the age of onset, age at diagnosis, sex and length of education. The comparison between AD TBI+ and bvFTD TBI+ groups showed that the onset age in AD TBI+ group was higher (65.81 years) than in the bvFTD TBI+ group (55.34 years) with a p value of 0.035 (B=5.486), adjusted with age and sex. The age of diagnosis was also different (68.46 years in AD and 62.79 years in bvFTD) with a p value of 0.017 (B=6.120), adjusted with sex. No statistically significant differences were found comparing sex and length of education between these groups.

Table 1: Characteristics of the study cohort and prevalence of prior TBI in each group

	FTD (n=222)	**AD (n=214)**	**Controls (HC) (n=100)**
Age at onset in years, mean (SD) **FTD vs AD: p<.001, B=3.793**	60.8 (11.2)	64.6 (9.3)	-
Age at diagnosis in years, mean (SD) **FTD vs AD: p=.004, B=2.355** **FTD vs HC:p=.894, B=-.140**	64.4 (8.2)	66.8 (8.9)	64.3 (9.8)
Sex, M % **FTD vs AD: p=.955, OR=1.011** **FTD vs HC: p=.237, OR=1.332**	51.4 (n=114)	51.4 (n=110)	44.0 (n=44)
FTD phenotype			

bvFTD **nfvPPA** **svPPA** **FTD-MND** **PSP**	141 44 9 23 1		
Education in years, mean (SD) **FTD vs AD: p=.037, B=.735** **FTD vs HC: p=.092, B=.698**	9.6 (3.3)	10.1 (3.5)	10.3 (3.4)
Family history of dementia (GS 1-3) or mutation (%) **FTD vs AD: p=.025, OR=.646** **FTD vs HC: p=.002, OR=.441**	52.3	40.2	32.6
***C9orf72* repeat expansion carriers %**	26.1 (n=58)	-	-
Previous TBI (%) **FTD vs AD: p=0.050, OR = 0.586** **FTD vs HC: p=0.108, OR = 0.566**	19.3 (n=42)	13.1 (n=28)	12.0 (n=12)

Abbreviations: AD = Alzheimer's disease; bvFTD = behavioral variant frontotemporal dementia; FTD = frontotemporal dementia; FTD-MND = frontotemporal dementia with motor neuron disease; GS = Goldman score; M = male; nfvPPA = non-fluent variant of primary progressive aphasia; n = number of cases; PSP = progressive supranuclear palsy; svPPA=semantic variant of primary progressive aphasia; TBI = traumatic brain injury

In the subgroup of *C9orf72* repeat expansion non-carrying FTD patients, TBI+ patients were younger at the time of the disease onset compared to TBI- patients (mean age 53.7 vs. 64.2 years, p <.001, B = 5.081). In the subgroup of *C9orf72* repeat expansion-carrying FTD patients, no statistically significant difference between TBI+ and TBI- groups regarding onset age (54.8 vs 58.2 years, p = 0.358, B = -2.446, respectively) was observed. Detailed demographics of the *C9orf72* repeat expansion carriers and non-carriers are shown in Table 2.

Table 2: Comparisons between *C9orf72* repeat expansion carriers and non-carriers

	C9+ FTD (n=58)	**C9- FTD (n=120)**
Age at onset in years, mean (SD)	57.9 (9.0)	61.6 (8.6)

C9+ vs C9-: p=.028, B=3.675		
Age at diagnosis in years, mean (SD) **C9+ vs C9-: p=.005, B=3.619**	61.3 (7.5)	65.0 (8.1)
Disease duration (onset to death, years, mean (SD) **C9+ vs C9-: p=.745, B=-.404**	7.8 (7.9)	7.8 (4.1)
Disease duration (diagnosis to death) years, mean (SD) **C9+ vs C9-: p=.121, B=1.319**	4.5 (3.4)	5.5 (3.3)
Gender, M % **C9+ vs C9-: p=.491, OR=.803**	47.5	51.7
Phenotype, %		
bvFTD	69.0 (n=40)	58.3 (n=70)
nfvPPA	12.1 (n=7)	26.7 (n=32)
svPPA	0.0 (n=0)	5.8 (n=7)
FTD-MND	19.0 (n=11)	8.3 (n=10)
PSP	0.0 (n=0)	0.8 (n=1)
Previous TBI, % ***p=0.003, OR=5.109**	8.6 (n=5) *	25.0 (n=30) *

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; FTD = frontotemporal dementia; FTD-MND = frontotemporal dementia with motor neuron disease; M = male; nfvPPA = non-fluent variant of primary progressive aphasia; n = number of cases; PSP = progressive supranuclear palsy; svPPA=semantic variant of primary progressive aphasia; TBI = traumatic brain injury

DISCUSSION

In the present study, we show that previous TBI is associated especially with sporadic FTD cases and an earlier age at onset of the disease in these patients. Our findings are in line with a previous report, in which earlier age at symptom onset in TBI+ FTD patients has also been reported. However, in that study, no genetic data were available [17]. To our knowledge, this is the first study evaluating the correlation of preceding TBI and the risk of FTD in Scandinavia or Northern Europe and including genetic data of the most common genetic alteration causing FTD. Because *C9orf72* repeat expansion is exceptionally common in Scandinavia and Northern Europe, we evaluated the association of previous TBI with age at onset also separately in the *C9orf72* repeat expansion carriers and non-

carriers. Interestingly, previous TBI was more prevalent in the group of patients without the *C9orf72* repeat expansion compared to the *C9orf72* repeat expansion carrier group. According to our data, previous TBI appears to result in an earlier age at onset in *C9orf72* repeat expansion non-carriers. Similar statistically significant correlation was not observed in the *C9orf72* repeat expansion carriers, although also in this group, TBI+ patients showed a trend of a younger onset age (mean onset age 54.8 years in TBI+ group vs. 58.2 years in TBI- group). It is possible that the trend towards an earlier onset in the *C9orf72* repeat expansion carriers remains non-significant due to limited statistical power in the group of this size. However, the *C9orf72* repeat expansion-carrying patients may be genetically vulnerable to dementia as they already carry a predisposing genetic background and are therefore more susceptible to develop dementia, even without preceding TBI.

Several previous studies have addressed whether TBI is an external risk factor for dementias in general but there are only a few studies especially evaluating the possible association between previous TBI and the risk for FTD. In one study, previous TBI was reported to be more prevalent among the FTD patients compared to controls with normal cognition (OR 1.67). However, in that study, previous TBI did not affect the age at onset when patients with and without previous TBI were compared [13]. Another study reported that TBI increased the risk for several types of dementia in a large cohort of male veterans. The risk of dementia was reported to be 60 % higher in individuals who had suffered from a previous TBI [26]. However, their study only included males and it is unclear whether the TBIs of the study participants had happened under military or civilian situations and, therefore, may not be generalized. In line with our study, a few other studies with retrospective settings have also shown an association between previous TBI and FTD [14], [16].

Based on our study, previous TBI was more common in FTD patient group compared to the neurodegenerative disease reference group of AD patients, even though also AD has been associated with a high prevalence of TBI in several studies [27]–[30]. The possible cellular and molecular mechanisms of TBI-induced neurodegeneration are still largely unclear. Interestingly, a study

utilizing *Drosophila* expressing mutations in *C9orf72* or fused in sarcoma (FUS) reported that head trauma induced the formation of stress granules that persisted even after 24 hours of the TBI and were dependent on the degree (20, 60 or 90° angles) and number of TBIs introduced [31]. The stress granules were shown to be positive for TAR DNA-binding protein 43 (TDP-43), which is a protein characteristically found in the cellular inclusions in the central nervous system (CNS) of both ALS and FTD patients [32][33]. Mutations causing progranulin (*PGRN*) gene loss-of-function are also a common cause of FTD characterized by TDP-43 brain pathology, and these patients show lowered plasma progranulin levels. It has been suggested that TBI may increase the risk of FTD by altering *PGRN* expression via a pathway including microglia-derived cytokines, such as elastases, which in turn can alter progranulin protein function and lead to impaired repair function in the CNS [34].

One possible mechanism of the especially strong association between TBI and FTD is that the disease mainly affects the temporal and frontal brain regions, which are more susceptible for traumatic injuries [7]. Thus, TBIs may more likely produce disturbances in the frontal and temporal lobes, which might be associated with their degeneration. Another possible explanation is that TBI does not directly impact the pathophysiological processes of FTD, but lowers brain/cognitive reserve, increasing the likelihood of having a neurodegenerative process clinically manifest at an earlier age. Finally, studies have demonstrated tau and TDP-43 proteinopathies in patients with chronic traumatic encephalopathy (CTE) with several TBIs in the past [7], [8], which raises the question, whether it is possible that head trauma initiates certain molecular cascades which initially lead to clinical FTD via these proteinopathies, but the exact mechanisms are still unknown.

We recognize that the limitation of this work is the retrospective setting of the study and the lack of neuropathological assessment of the patients. The limited group size most likely resulted in lack of statistical power (and lack of statistically significant differences) between the HC group and FTD / AD groups. Further, our dataset did not enable us to accurately specify the exact occasion and stage of the TBI for all the cases, and thus we were not able to make sufficient sub-analyses regarding the

role of these factors. Notably, head traumas that were reported to have occurred clearly after the reported disease onset were not included, as the emphasis was to consider head trauma as a risk factor for the disease or its onset. The strengths of our study are the well-characterized cohorts with thoroughly examined patients, inclusion of genetic data, and the fact that the clinical diagnoses have been made in special-level neurodegeneration outpatient clinics.

Conclusion: Our study shows that prior TBI is associated with the development of FTD, especially sporadic variants and with earlier onset of symptoms. Prior TBI may lower the onset age also in *C9orf72* repeat expansion-carrying FTD patients, but examination of larger patient cohorts in the future studies are required for enabling the detection of statistically significant differences between the study groups and confirming this hypothesis. Nevertheless, the present findings suggest that TBI may be a triggering factor for the neurodegenerative processes in FTD brain, but clarifying the precise underlying mechanisms still needs further studies.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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ETHICS APPROVAL

The ethics committees of the Northern Ostrobothnia Hospital district and Northern Savo Hospital district approved the study. The study was performed in accordance with the Declaration of Helsinki.

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