ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 12, Issue, 01, pp.9673-9678, January, 2020

DOI: https://doi.org/10.24941/ijcr.37710.01.2020

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA RELATED TO TRAUMATIC BRAIN INJURY

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ARTICLE INFO

Article History:
Received 04th October, 2019
Received in revised form
15th November, 2019
Accepted 19th December, 2019
Published online 30th January, 2020

Key Words:

Frontotemporal Dementia, Traumatic Brain Injury, Behavior,
Personality.

ABSTRACT

Introduction: Frontotemporal dementia (FTD) is one of the leading causes of neurodegenerative dementia in people under 60 years old. Traumatic brain injury (TBI) is the most well-established environmental risk factor for dementia. **Case Report**: We present a case of 59-year-old male patient with 3 years history of behavioral abnormalities and personality changes with gradual onset. He had history of severe TBI about 20 years before the initial presentation, in which he needed a surgery for intracranial hemorrhage evacuation.The neuropsychological examination showed perseveration, impairment in executive function, verbal and visual memory and visuospatial. He was cooperative during examination but sometimes would show inappropriate and bizarre behavior toward the examiner. The MRI Brain result showed frontal and temporal atrophy. The patient was given symptomatic treatment, as there was no approved pharmacological therapy for FTD. **Discussion**: Behavioral changes are the presenting feature and dominate the clinical picture throughout the disease course. This patient was diagnosed with FTD because of the progressive abnormality of the behavior along with personality change. The imaging results showed lesions that caused by the TBI which happened almost 20 years before the initial symptom but also showed frontal and anterior temporal atrophy. In the absence of definitive biomarkers, the diagnosis of bvFTD is dependent on clinical diagnostic criteria. **Conclusion**: The present study emphasized the importance of a detailed history and neurological examination, including neuropsychological examination and brain imaging in the case of middle-aged patients with insidious onset of personality changes and behavior problems.

Citation: ***Fasihah Irfani Fitri.*** **2020.** "Behavioral variant frontotemporal dementia related to traumatic brain injury", *International Journal of Current Research*, 12, (01), 9673-9678.

INTRODUCTION

Traumatic brain injury (TBI) is the most well-established environmental risk factor for dementia (Ramalho, 2015; Shively, 2012; Rosso et al., 2003). Currently available data suggest: (1) sufficient evidence of an association between moderate/severe TBI and dementia, with an increased risk of dementia of between 2 and 4 fold for these patients; (2) limited evidence of an association between mild TBI with loss of consciousness (LOC) and dementia; (3) and inadequate/insufficient evidence to determine whether an association exists between mild TBI without LOC and dementia (Ramalho, 2015). A meta-analysis of 15 case-control studies estimated that individuals who had had a head injury of sufficient severity to result in LOC were at approximately 50% increased risk of dementia compared with others (pooled OR 1.58; 95%CI 1.21-2.06) (Shively, 2012; Rosso, 2003; Fleminger, 2003). Frontotemporal dementia (FTD) is one of the leading causes of neurodegenerative dementia in people under 60 years old (Deutsch, 2015).

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Known risk factor of FTD are positive family history of FTD, head injury and thyroid disease (Kugu, 2010). TBI remains the only established environmental risk factor of FTD (Rosso, 2003; Jawaid, 2009). A retrospective case-control analysis of 80 patients with sporadic FTD and 124 matched controls showed that head trauma was associated with an odds ratio of 3.3 (95% CI 1.3 to 8.1). The time between head trauma and the onset of dementia spaned several decades in some patients (Rosso et al., 2003). Remote TBI (> 1 year prior to assessment) with extended LOC was associated with an increased risk of FTD (OR 1.67, 95% CI: 1.004-2.778). TBI also influenced clinical symptomatology and severity in FTD subtypes. These findings emerged after excluding data from participants with recent/active TBI or TBI resulting in chronic neurological deficits, suggesting that they were not simply a direct consequence of TBI-related brain dysfunction, but potentially arised from the precipitation and/or acceleration of subsequent neurodegenerative disease (Deutsch, 2015). A restrospective study of 678 behavioral variant FTD (bvFTD) patients showed that TBI history with LOC occuring more than one year prior to diagnosis is associated with an earlier age of symptom onset and age of diagnosis (2.8 and 3.2 years, respectively), and

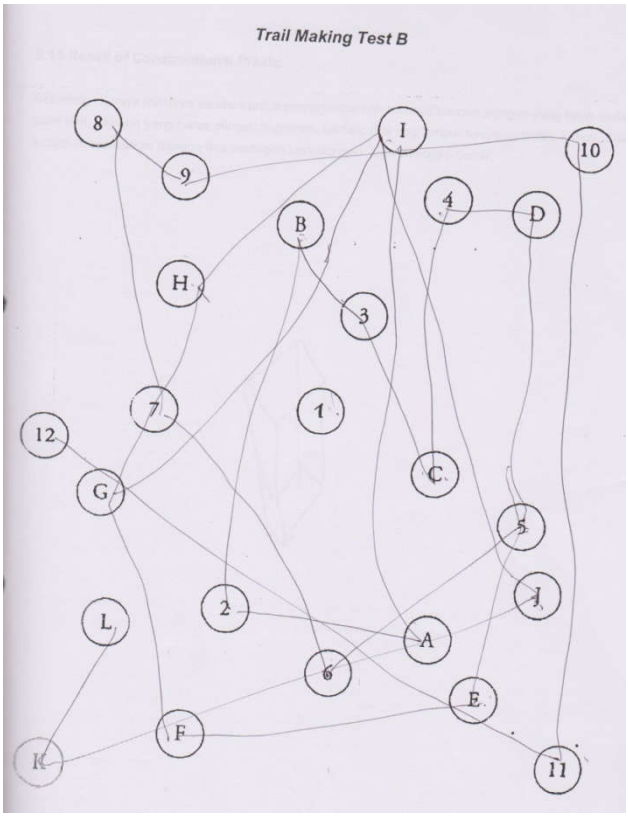

Figure 1. Trail Making Test B

these effects were independent of family history of dementia and education (LoBue, 2016). In Lund and Manchester group clinical and neuropathological research criteria of FTD, a past history of head trauma related to the onset of dementia is one of the diagnostic exclusion features (The Lund and Manchester Groups, 1994). However establishing the exact association of head injury and the onset of dementia in clinical practice is often difficult, especially after a long latency. Yokota et al (2001) reported an autopsy caseof TBI presenting as FTD wth Klüver-Bucy syndrome after a one-year latency period. The histopathological examination revealed small cerebral contusions in the bilateral temporal lobe with loss of myelin and axons. The laminar structure in the frontotemporal cortex was well preserved. From the pathological features, the case was diagnosed as TBI (Yokota, 2001). The International consensus criteria for bvFTD did not list a history of TBI as one of the exclusion criteria. In this criteria, the exclusionary criteria are: pattern of deficit is better accounted for by other non-degenerative nervous system or medical disorders; behavioral disturbance is better accounted for by a psychiatric diagnosis; and biomarkers strongly indicatve of AD or other neurodegenerative process (Rascovsky, 2011). Here we present a case of 59-year-old male patient with 3 years history of behavioral abnormalities and personality changes with gradual onset. He had history of severe TBI about 20 years before the initial presentation, in which he needed a surgery for intracranial hemorrhage evacuation. We describe the neuropsychological profiles and treatment, along with the review of the literature.

CASE REPORT

A 59-year-old male patient presented with behavioral abnormalities and personality changes of gradual onset over the last 3 years. He was brought to consultation by his wife who had concerns on his behavior because it was getting worse and interfered with his daily living. As the patient was not able to give accurate history, his wife was interviewed and it was found that the patient has had personality change for 3 years now. The onset was insidious and progressively worsening. She noticed that patient became more apathy, had loss of motivation, drive and interest in doing most of the daily activities. He no longer seemed to be interested in his job and hobbies. The patient owned a mini store so he used to spend most of his time running the store himself, doing the shopping and managing the finance and other necessary things, but he would prefer to stay at home and had to be reminded to go to the store almost every day for the last three years. His wife first thought that he was only feeling bored or tired so she took over his tasks. He also became indifferent and no longer participated in any social acitivities. Again, his wife thought only because he was only feeling lazy and tired. He also had problems with memory, particularly short-term memory. He had poor judgement and diminished problem-solving skills. The changes in behavior were brought into his wife attention when it almost caused an accident. When he drove a vehicle he would suddenly stopped and seemed confused about driving a vehicle. His wife was getting even worried about the symptoms about 2 years ago when the patient forgot to turn off the stove that was almost made the house on fire. But when he was asked about the incident he could not remember what happened and denied that he had turned on the stove in the first place. He became very upset when he was confronted about that incident.

The patient could still recognize family members, but he immediately forgot his son in law after he had married his daughter. He got so angry and told his wife that their daughter had brought a stranger to their home to live together. For the last one year he became more reserved and communicated poorly with family members and were sometimes found to be non-responsive to questions. His wife also noticed that he had peculiar behavior such as smiling to himself, grinning without apparent cause and would sometimes repeated a sentence ar a word in answering to a question. Sometimes he had visual hallucinations of people working near the house and would repeatedly scream to make them go away, then he would become agitated for a while. There was a history of severe head injury about 20 years ago in which he needed surgery for an intracranial hemorrhage evacuation, but his wife did not keep the imaging or other results of examination from this admission. His wife said that after the accident and the surgery the patient did not have any subjective cognitive complaint or other changes in behavior until 3 years ago with the symptoms described above. On examination the patient was alert and conscious with GCS 15. His blood pressure was 120/80 mmHg, pulse rate 80 beats per min and had no fever. All cranial nerves were found to be intact. Examinations for respiratory, cardiovascular, gastrointestinal and musculoskeletal systems were essentially normal. He was fully attentive and cooperated but his affect was blunt. He had no insight of his condition. Speech was normal but at times patient would become mute and sometimes said a sentence repeatedly as a response to a question, such as 'RCTI oke' (a tag line of one national television channel). He made good eye contact but most of the time needed to be asked repeatedly and he would say that he could not answer a question because it was a secret he needed to keep. His forward digit span was 6 and his backward digit span was 4. His mini mental state examination (MMSE) was 17/30, with abnormal scores on time orientation (0/5), place orientation (1/5), recall (0/3), copy of pentagon (0/1).

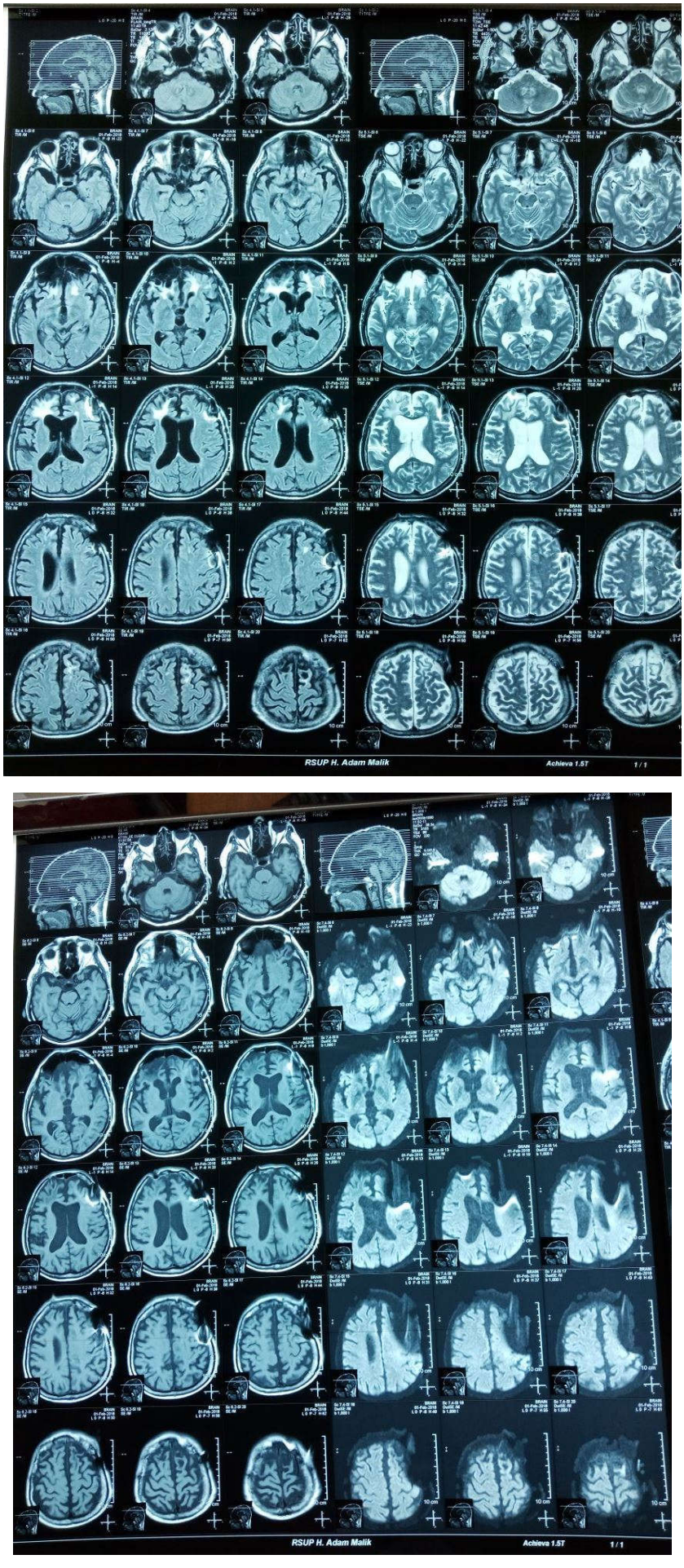
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Figure 2. MRI

International consensus criteria for behavioural variant FTD

I. Neurodegenerative disease
The following symptom must be present to meet criteria for bvFTD
- A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD
Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.
- A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
  - A.1. Socially inappropriate behaviour
  - A.2. Loss of manners or decorum
  - A.3. Impulsive, rash or careless actions
- B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
  - B.1. Apathy
  - B.2. Inertia
- C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
  - C.1. Diminished response to other people's needs and feelings
  - C.2. Diminished social interest, interrelatedness or personal warmth
- D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
  - D.1. Simple repetitive movements
  - D.2. Complex, compulsive or ritualistic behaviours
  - D.3. Stereotypy of speech
- E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
  - E.1. Altered food preferences
  - E.2. Binge eating, increased consumption of alcohol or cigarettes
  - E.3. Oral exploration or consumption of inedible objects
- F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
  - F.1. Deficits in executive tasks
  - F.2. Relative sparing of episodic memory
  - F.3. Relative sparing of visuospatial skills

III. Probable bvFTD
All of the following symptoms (A–C) must be present to meet criteria.
- A. Meets criteria for possible bvFTD
- B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)
- C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
  - C.1. Frontal and/or anterior temporal atrophy on MRI or CT
  - C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioural variant FTD with definite FTLD Pathology
Criterion A and either criterion B or C must be present to meet criteria.
- A. Meets criteria for possible or probable bvFTD
- B. Histopathological evidence of FTLD on biopsy or at post-mortem
- C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD
Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.
- A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
- B. Behavioural disturbance is better accounted for by a psychiatric diagnosis
- C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

Figure 2. Rascovsky et al. Sensitivity of revised diagnostic criteria for the behavioral variant of frontotemporal dementia Brain 2011:(134): 2456-2477

At this time the affected domains were memory and visuospatial that did not suit the 'common"neuropsychological profile of FTD which usually affect executive fuction, with relative sparing of memory and visuospatial domains. So we performed more detailed neuropsychological examinations as listed in CERAD. The results were as follow: Word list memory task was 10 (2,3,5 on first, second and third trial respectively), constructional praxis was 8, verbal fluency was 14, Boston Naming Test was 14, word list recall was 3 and word list recognition was 5.5. The CERAD score was 54.5. Trail Making Test A was performed in 85 seconds without error, but the patient could not perform the Trail Making Test B. He finished it in 187 seconds but with so many errors and could not fix the mistake he made immediately. Recall of constructional praxis was only 1. He only drew the cube but he could not draw it right as it should. His AD8 score was 8 (his wife noticed changes in all of the questions). Score of acitivity daily living was 3 and his IADL score was 10. He needed help in doing most of the daily task especially those that require higher cognitice function such as finance, shopping and handling complex tasks. His clinical dementia rating scale was 2 and the Abe BPSD score was 6 (hallucinations and apathy/indifference). The MRI Brain result showed hypointense lesion on T1, T2, FLAIR, DWI on the right frontal lobe and hypointense lesion on T1 , hyperintense on T2, FLAIR on bilateral frontal lobes, and cerebral atrophy. Patient's full blood count, renal functions, thyroid functions, liver functions, serum electrolytes and routine urine examinations was normal. The patient was already taking antipsychotic at that time (Risperidone 2 mg once daily) for about two weeks.

The differential diagnoses at that time was frontotemporal dementia because of the prominent of the behavior symptoms. The patient was given SSRI (Fluoxetin 10 mg once daily) and acetylcholinesterase inhibitor (donepezil started at 5 mg once daily for two weeks than it was gradually increased to 10 mg once daily). His wife refused to stop the antipsychotic treatment at that time because she was worried that her husband would become agitated and had hallucinations. After 3 months of therapy his cognitive symptoms did not improve significantly but the behavior symptoms gradually improved so the antipsychotic therapy was stopped.

DISCUSSION

FTD is the most common of a group of clinical syndromes associated with degeneration of the prefrontal and anterior temporal lobes which has been called frontotemporal lobe degeneration (FTLD). Behavioral changes are the presenting feature and dominate the clinical picture throughout the disease course. Qualitative changes in language and cognitive impairments in executive function also occur. The absence of early neurological signs and findings of focal abnormalities in the frontotemporal lobes on neuroimaging contributeto the clinical dianosis. FTLD comprises atrophy of the prefrontal and anterior temporal neocortex. Differences in topographical distribution of atrophy determine the clinical syndromes of FTD, semantic dementia and progressive aphasia (Neary, 2005). The behavioural variant of frontotemporal dementia (bvFTD) is a clinical syndrome characterized by a progressive deterioration of personality, social behavior and cognition.

These changes result from frontotemporal lobar degeneration associated with a range of heterogeneous pathologies

(Rascovsky, 2011). It has an insidious onset, typically unfolding over many years. The biological damage involved in neurodegeneration progresses in a latent phase until a threshold is reached, at which point cognitive/behavioral impairments become clinically manifest. As such, by the time dementia is diagnosed, the time between onset of the biological damage and its clinical manifestation may be many years apart (LoBue, 2016). This patient was diagnosed with FTD because of the progressive abnormality of the behavior along with personality change. He had early apathy and inertia, early diminished social interest and stereotyped speech, early emotional blunting and loss of insight, although the patient did not show early behavioral disinhibition and hyperorality. The imaging results showed lesions that caused by the TBI which happened almost 20 years before the initial symptom but also showed frontal and anterior temporal atrophy. In the absence of definitive biomarkers, the diagnosis of bvFTD is dependent on clinical diagnostic criteria; in other words, the identification of the syndrome's core or necessary symptoms (Rascovsky, 2011). There are several diagnostic criteria for FTD, developed by Lund and Manchester, Neary and colleagues, and the most recent was from The International Behavioural Variant FTD Criteria Consortium (FTDC) that developed revised guidelines for the diagnosis of bvFTD (Rascovsky, 2011; Pijnenburg, 2011). According to the International consensus criteria for bvFTD (figure 3) this casewould still possibly be classified to Probable FTD, because it consisted of 3 out of 6 criteria and the patient exhibited significant functional decline and the imaging results showed frontal and/or anterior temporal atrophy. The confusing facts were the neuropsychological profiles that showed impairment in episodic memory and visuospatial skills that should be relativle spared in FTD according to that criteria.

The history of TBI in this patient raised a question whether it was associated with the clinical presentation or not, because the time span between the TBI and the onset of dementia was relative far (almost 20 years). His wife also did not notice any symptom or change in behavior after the TBI at the first place. The relationship between TBI and FTD has been studied quiet extensively (Ramalho, 2015; Shively, 2012; Deutsch, 2015; Jawaid, 2009; LoBue, 2016). TBI is known to cause neuronal and axonal injury and result in a cascade of abnormal neurochemical processes and anatomically, bvFTD involves degeneration primarily in the frontal lobes and the anterior temporal regions, and TBI has a well-known predilection for affecting these regions and their underlying connections (LoBue, 2016). TBI initiates an inflammatory cascade that results in the release of amino acids, such as glutamate and aspartate, and free radicals that lead to tissue damage.[1]TBI may promote the development of FTD through its effects on microglial activation, which can lead to progranulin deficiency. Progranulin appears to play a role in neuronal growth and repair, and acquired progranulin deficiency could precipitate neurodegeneration, similar to the progranulin deficiency that arses from PGRN mutations associated with FTD. Since the frontal and temporal lobes are particularly susceptible to damage in TBI, these regions may also be particularly susceptible to TBI-related progranulin depletion (Deutsch, 2015). Frontotemporal lobar degeneration (FTLD) with neuronal inclusions of the TAR-DNA-binding protein 43 (TDP-43) is the most common pathological subtype of FTLD (FTLD-TDP). Mutations leading to a loss of function in the progranulin gene (PGRN) are the most common cause of FTLD-TDP (Jawaid et al., 2009). It has been hypothesized that release of elastases by microglia during CNS injury or inflammation may cleave PGRN into proinflammatory GRNs. This cleavage may be inhibited by secretary leukocyte protease inhibitor released by astrocytes. An increase in elastase levels is also likely after TBI as it leads to activation of microglia, which in turn secrete multiple cytokines including elastase. This raises the possibility that TBI may cause an increase in elastases, which would result is a reduction in the levels of PGRN and an increase in the proinflammatory GRNs. Hence, TBI can potentially induce a 'PGRN insufficiency' state leading to a greater susceptibility to FTD. The role of TBI in the pathogenesis of FTD is also likely to be multifactorial and the lowered levels of PGRN might just be one element (Jawaid, 2009). In rodent models, TBI resulted in neurodegeneration and progressive brain atrophy that continued for at least 1 year after injury. Several proteins associated with neurodegenerative disease in humans have also been demonstrated to accumulate following experimental TBI in rodents. Amyloid precursor protein is upregulaed immediately after TBI and β-amyloid peptide accumulate over weeks and months after trauma. β-secretase, presenilin 1 and caspase 3 also accumulate for up to 6 months after injury. TBI resulted in accumulations of intra-axonal β-amyloid peptide and hyperphosphorylated tau which persisted for up to 1 week after injury. These findings have led to the hypothesis that β-amyloid peptide and tau accumulations are important mechanisms in the long-term neurodegenerative effects of TBI (Ramalho, 2015; Shively, 2012).

Conclusion

Although the association between TBI and the clinical symptoms of FTD in this patient can not be precisely established, the present study emphasized the importance of a detailed history and neurological examination, including neuropsychological examination and brain imaging in the case of middle-aged patients with insidious onset of personality changes and behavior problems.

Glossary of Abbreviations

bvFTD: Behavioral frontotemporal dementia
FTD: Frontotemporal dementia
FTLD : Frontotemporal lobe degeneration
PGRN: Progranulin
TBI: Traumatic brain injury
TDP-43: TAR-DNA-binding protein 43

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