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WHITE MATTER TRACT SIGNATURES ON DIFFUSION TENSOR IMAGING (DTI) AS AN AID TO CONFIRM THE DIAGNOSIS OF THE BEHAVIORAL VARIANT OF FRONTOTEMPORAL DEMENTIA (BVFTD) – A REVIEW OF THE LITERATURE.

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ABSTRACT

Objective: Behavioral variant of Frontotemporal Dementia (bvFTD) is often misdiagnosed as a primary psychiatric disorder. It is therefore imperative to confirm the diagnosis of bvFTD as early as possible so that the patients may benefit from evidence-based treatments.

Data Source: 11 studies related to the topic were found out of which seven were selected for this review.

Data Extraction: The data from the selected seven studies was extracted.

Data Synthesis: All the studies were case-control studies, published during 2013-2015 and used the International Consensus Criteria for the diagnosis of bvFTD. All studies reported specific white matter tract changes on DTI in bvFTD.

Conclusion: White matter signatures on DTI are a core feature for the confirmation of the diagnosis of bvFTD. It helps in the comparison between dementias and monitoring of bvFTD.

KEYWORDS : "White matter tract signatures", "Diffusion Tensor Imaging" and "behavioral variant of Frontotemporal Dementia".

INTRODUCTION:

BvFTD is a subtype of Frontotemporal Dementia which characteristically manifests initially as behavioral and personality changes before the cognitive changes appear. These changes include disinhibitions, overeating, compulsions, loss of empathy and apathy. This often leads to the misdiagnosis of bvFTD as a primary psychiatric disorder[1]. It is therefore imperative to confirm the diagnosis of bvFTD as early as possible so that the patients may benefit from evidence-based treatments.

Several investigations, such as EEG (Electroencephalography)[2] , BOLD (Blood Oxygenation Level Dependent[3]) - and ASL(Arterial Spin Labeling[4])-fMRI(functional Magnetic Resonance Imaging), FDG (Fludeoxyglucose)-PET(Positron Emission Tomography)[4] CSF analysis of proteins[5] and DTI(Diffusion Tensor Imaging[6], have been found to be useful in the diagnosis of bvFTD. Out of these, DTI has proven to be the most suitable neuroimaging modality which could aid in the confirmation of the diagnosis of bvFTD.

DTI (Diffusion Tensor Imaging) is a special kind of diffusion-weighted Magnetic Resonance Imaging that measures the diffusion of water molecules within biological tissue to assess disruption of white matter microstructure in terms of axonal density, cytoskeletal structure and myelin integrity.

DTI studies show specific changes in white matter tracts in terms of disintegration of these tracts in patients of bvFTD. These changes have been referred to as white matter tract signatures.

The definitive involvement of specific white matter bundles consistently across patients of bvFTD highlights the role of white matter tract signatures as a potential biomarker for confirmation of diagnosis of bvFTD.

Hence, we reviewed the literature, regarding white matter tract signatures in DTI as an aid to the confirmation of the diagnosis of bvFTD.

METHOD:

A comprehensive electronic search was conducted on PubMed using a combination of the following search terms: "bvFTD" AND "Diffusion tensor imaging" AND "white matter changes" AND "biomarkers". 11 studies related to the topic were found out of which seven were selected for this review. We included only those studies that described white matter signatures on diffusion tensor imaging as a significant biomarker for the diagnosis of bvFTD.

Studies that did not adopt the International Consensus Criteria for the diagnosis of bvFTD, studies conducted before 2013 and studies that did not include all parameters of DTI, namely, Axial Diffusivity, Radial Diffusivity, Mean Diffusivity (or Trace Diffusivity = 3*MD) and Fractional Anisotropy were excluded from the review.

The data from the selected seven studies was extracted under the following headings: year of study, author, study design, sample size, criteria for diagnosis of bvFTD, parameters of DTI, tracts delineated in the bvFTD group and DTI in the confirmation of the diagnosis of bvFTD. The results were tabulated and analysis of the data was done.

RESULTS:

Seven studies reported the white matter tract signatures in DTI as a confirmation for the diagnosis of bvFTD.

Year of publication – All the studies were published during 2013-2015. One study was published in 2013[7], two in 2014[6][8], and four studies were published in 2015[9][10][11][12].

Study design – Five out of the seven studies were cross-sectional case-control studies and two of them were prospective case-control studies.

Diagnostic criteria for bvFTD – All the studies used the International Consensus Criteria for the diagnosis of bvFTD developed by the International Behavioral Variant FTD Criteria Consortium (FTDC).

Parameters of DTI assessed –All the studies assessed white matter tract changes using all four parameters of DTI, namely, Radial Diffusivity, Mean diffusivity (Trace Diffusivity/3), Axial Diffusivity and Fractional Anisotropy.

Specific White Matter tract changes –Six of the studies identified changes in the Uncinate Fasciculus and Corpus Callosum[6][8][9][10][11][12]. Three of these studies reported changes in the head[8][9][12] while one showed changes in the body[10] of the corpus callosum. Six studies identified changes in the Cingulum bundles[6][7][8][10][11][12]. Four studies identified changes in the Anterior Thalamic Radiation[6][8][9][12]. Some of the studies also found changes in some minor white matter tracts. Four studies found changes in the SLF[6][8][9][12], three within the ILF[6][8][11], three within the IFO[8][9][12], three in the Fornix[6][9][11] and one in the Forceps Minor[9].

DTI in the confirmation of the diagnosis of bvFTD– Four of the seven studies reported white matter tract changes specific to bvFTD[6][8][11][12]. One study highlighted the role of white matter changes in DTI as an aid in differentiating between bvFTD patients and Alzheimer's disease patients[9]. One study reported the role of Cingulum bundle changes as helpful in the diagnosis of bvFTD[7]. One longitudinal study emphasized the role of white matter changes in DTI as an aid in the monitoring of the progress of bvFTD[10].

DISCUSSION:

BvFTD is a disorder which is commonly misdiagnosed as a primary psychiatric syndrome due to the considerable overlap of behavioral and neurological symptoms. Creating neuroimaging markers would aid in confirming the diagnosis of bvFTD. This would help in the confirmation of diagnosis of bvFTD and enable subsequent treatment. White matter tract analysis using Diffusion Tensor Imaging has revealed a characteristic pattern of white matter tract signature in bvFTD patients.

Seven studies were included in our review and the information extracted from these studies has revealed a clearer picture about the white matter tract involvements in bvFTD. A generalized finding of involvement of the Uncinate Fasciculus, Corpus Callosum and the Cingulum bundles across majority of the studies creates a possibility of drawing a neuroimaging profile of bvFTD which could aid in the confirmation of diagnosis.

Strengths- Our review examined seven well-designed studies which used the International Consensus Criteria for diagnosis of bvFTD. Only studies with the four important DTI parameters (AD, MD, RD and FA) were used for the assessment of the white matter tract changes. A clearer picture emerges about white matter changes in DTI for the confirmation of diagnosis of bvFTD. Our review also shows that white matter changes also help in differentiating bvFTD from other conditions such as Alzheimer's and other FTD subtypes.

Limitations- Studies on white matter changes in DTI for the confirmation of the diagnosis of bvFTD were rare and were difficult to locate in the literature. We could have missed a few studies in our search. Studies in languages other than English were excluded. The data in the various studies was heterogeneous in nature.

Conclusion:

All studies were published during 2013-2015 and were case-control studies. All used the International Consensus Criteria for the diagnosis of bvFTD and used all four parameters of DTI (AD, MD, RD and FA) for assessment of white matter tract changes. The presence of a unique white matter signature could be observed by studying tract degeneration on DTI. The Cingulum Bundles, Corpus Callosum and the Uncinate Fasciculus are the most commonly involved tracts which may be defined as the core of the neuroimaging profile in bvFTD patients. Other tracts such as the ATR, ILF and SLF, IFO, Forceps Minor and the Fornix have been shown to be involved in some of the studies. This white matter tract signature has been shown to be specific to bvFTD and is a core feature of this syndrome. It therefore assists in the confirmation of diagnosis of bvFTD. It also helps in a more precise diagnosis between bvFTD and other dementias such as Alzheimer's or other subtypes of FTD. White matter tract signature can also aid in disease monitoring in bvFTD.

Implications:

Our review has important implications for mental health services, training of mental health professionals and research. White matter signatures in DTI are useful for the confirmation of the diagnosis of bvFTD and subsequent treatment of patients with bvFTD.

Table 1: White Matter Signatures on Diffusion Tensor Imaging in bvFTD and other dementias

Year of Study	Study Design	Number of Subjects	Diagnostic Criteria for bvFTD	Parameters of DTI assessed	Specific White Matter tract changes	DTI in the confirmation of the diagnosis of bvFTD
Daianu et al (2015)[12]	Case-Control	bvFTD = 20 EOAD = 23 Controls = 33	International Consensus Criteria	FA, RD, AD, MD	UNC, CC (frontal), ATR, Cingulum bundles, Lt. SLF, IFO	Specific network of white matter tracts are involved in the bvFTD spectrum.
Downey et al (2015) [11]	Case-Control	bvFTD = 29 svPPA = 15 Control = 37	International Consensus Criteria	FA, RD, AD, TR (3MD)	UNC, CC, Cingulum bundles, ILF, Fornix	White Matter changes in DTI can yield robust signatures in bvFTD and other FTD subtypes.
Mahoney et al (2015) [10]	Prospective Case-Control	bvFTD = 23 Control = 18	International Consensus Criteria	FA, RD, AD, MD	UNC, CC (body), Cingulum bundles	DTI is an important biomarker for disease monitoring in patients with bvFTD
Möller et al (2015) [9]	Case-Control	bvFTD = 30 AD = 39 Controls = 41	International Consensus Criteria	FA, RD, AD, MD	UNC, CC (frontal), ATR, SLF, IFO, Fornix, Forceps minor	DTI measures help in a more precise diagnosis between bvFTD & AD
Mahoney et al (2014) [6]	Case-Control	bvFTD = 27 AD = 25 Controls = 20	International Consensus Criteria	FA, RD, AD, TR (3MD)	UNC, CC, ATR, Cingulum bundles, SLF, ILF, Fornix	White matter signatures on DTI – a core feature of bvFTD
Lam et al (2014) [8]	Prospective Case-Control	bvFTD = 12 PNFA = 10 SD = 11 Controls = 15	International Consensus Criteria	FA, RD, AD, MD	UNC, CC (frontal), ATR, Cingulum bundles (anterior), SLF, ILF, IFO	Patterns of white matter changes are specific to bvFTD and other FTD subtypes.
Santillo et al (2013) [7]	Case-Control	bvFTD = 14 Control = 22	International Consensus Criteria	FA, RD, AD, MD	Cingulum bundles	White matter changes in the Cingulum is a powerful tool for diagnosing bvFTD

Abbreviations:

UNC – Uncinate Fasciculus
CC – Corpus Callosum
ATR – Anterior Thalamic Radiation
SLF – Superior Longitudinal Fasciculus
ILF – Inferior Longitudinal Fasciculus
IFO – Inferior Fronto-Occipital Fasciculus

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