The frontal lobe syndrome

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Part 3

THE LATE ONSET FRONTAL LOBE SYNDROME STUDY

Chapter 5

BUILDING A NEW PARADIGM FOR THE EARLY RECOGNITION OF BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA: THE LATE ONSET FRONTAL LOBE SYNDROME-STUDY (LOF-STUDY)

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ABSTRACT

Objectives: To describe the aims and design of the ongoing Late Onset Frontal lobe syndrome-study (LOF-study); a study on the spectrum of neurodegenerative and psychiatric etiologies causing behavioral changes in later life and on the role of Magnetic Resonance Imaging (MRI), [^{18}F]FDG- Positron emission tomography (PET) en cerebrospinal fluid (CSF)-biomarkers in predicting and identifying the different underlying pathologies with a special focus on the behavioral variant of frontotemporal dementia (bvFTD).

Methods: The LOF-study is an observational cross-sectional and prospective follow-up study. Patients aged 45 to 75 with frontal behavioral change consisting of apathy, disinhibition or compulsive / stereotypical behavior are being included (April 2011- 2013). Patients undergo a multidisciplinary assessment by a neurologist and psychiatrist, MRI, CSF and PET measurements at inclusion and after two years of follow-up.

Results: The diagnostic added value of MRI, PET and CSF-results and their predictive value will be measured after two years of follow up.

Conclusion: This is the first large scale prospective follow-up study of patients with late onset behavioral disorders.

INTRODUCTION

A late onset frontal lobe syndrome (LOF) is defined as apathy, disinhibition or compulsive / stereotypical behavior arising in middle or late adulthood. Different disorders such as behavioral variant of Frontotemporal dementia (bvFTD), psychiatric disorders like depression or schizophrenia, or other types of dementia may present with a LOF [1]. The main form of dementia presenting with a LOF is the bvFTD; a clinical syndrome resulting in progressive personality changes, behavioral disorders and cognitive deterioration.

The prevalence of FTD in the western world is estimated at 15-22 per 100.000 in the age group between 45 and 64 years [2]. In addition, FTD accounts for 9.7% of early onset dementia incidences [3]. The disease is associated with heterogeneous pathologies with overlapping presentations [4;5].

BvFTD symptoms are observed in many psychiatric disorders as well: apathy, emotional blunting, economy of speech and psychomotor retardation may be seen in depression and schizophrenia. Disinhibition may be present in manic episodes, kleptomania and bipolar disorder; stereotypical language or motor behavior may be a symptom in anxiety disorders, obsessive-compulsive disorder or tic syndromes [6]. Psychiatric disorders typically develop during adolescence or young adulthood, however, so-called *late-onset* and *very late-onset* disorders may also manifest during middle and old age [7].

Furthermore, other forms of dementia such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and vascular dementia (VaD) can all present themselves as a clinically apparent frontal lobe syndrome.

The overlap in clinical symptoms is caused by the involvement of the same fronto-subcortical circuits. This is illustrated by the fact that a high proportion of bvFTD patients initially receives a psychiatric diagnosis [8].

The International bvFTD Criteria Consortium (FTDC) has recently established new diagnostic criteria, as the sensitivity of the widely used Neary criteria for bvFTD was relatively limited [9-11]. In these revised criteria a degree of probability is assigned to the clinical diagnosis using neuroimaging. However, these newly proposed criteria do not solve the frequent diagnostic dilemma -diagnosing bvFTD or a psychiatric disorder-, because 5 of the 6 core criteria are based on behavioral symptoms. In addition, the criteria propose that if 'behavioral disturbance is better accounted for by a psychiatric diagnosis', a diagnosis of bvFTD is to be excluded [11]. The inclusion of neuroimaging and CSF results could improve diagnosis of bvFTD, however, the added value of these biomarkers remains to be established.

MRI scanning of the brain reveals disproportional lobar atrophy of the frontal and/or temporal lobes in 50-70% of bvFTD patients [12]. Using [^{18}F]FDG-PET with visual rating, sensitivity rises to a range from 81% up till 90% [12]. However, specificity of these methods is limited, since structural as well as functional neuroimaging in patients with

schizophrenia or depression have shown regional (frontal, temporal or hippocampal) atrophy or hypometabolism as well [13;14].

Measuring CSF levels of Amyloid-beta, total Tau and phosphorylated Tau is mainly helpful to distinguish FTD from Alzheimer's disease (AD), but no specific CSF biomarker profile has been associated with FTD [15].

Considering the great overlap in clinical presentation between neurodegenerative disorders and psychiatric diseases, identifying the etiology of the LOF may be difficult in clinical practice. It is essential to come to an early and accurate diagnosis, because neurodegenerative disorders are progressive and will eventually lead to death whereas most psychiatric disorders are treatable

Aim

This paper provides a description of the LOF study that aims to evaluate the spectrum of etiologies underlying LOF and to discern the bvFTD prodrome from the broadest clinically relevant differential diagnosis. An additional purpose is to examine the added value of MRI, [^{18}F]FDG-PET and CSF-biomarkers for bvFTD and its differential diagnosis. Finally, we aim to develop a multidisciplinary clinical paradigm enabling an early diagnosis of bvFTD.

METHODS

Design

The LOF-study (Late Onset Frontal lobe syndrome study) is an ongoing multi-center observational cross-sectional and prospective follow-up study. Patients are recruited through the memory clinic of the Alzheimer center of the VU Medical Centre and the department of Old Age psychiatry of the GGZInGeest (in- and out-patients), Amsterdam, the Netherlands, between April 2011 and April 2013.

Definition of the Late Onset Frontal Lobe Syndrome (LOF)

LOF is defined as behavioral change consisting of apathy, disinhibition and / or compulsive / stereotypical behavior arising in middle or late adulthood (observed by clinician or reliable informant).

Inclusion and exclusion criteria

Inclusion criteria are (1) age between 45 and 75; symptom onset between the age of 40 and 70, (2) Frontal Behavioral Inventory (FBI)-score of 11 or higher and / or a SRI Stereotypy Rating Inventory (SRI)-score of 10 or higher (See: Appendix 1 and 2 of this thesis).

Exclusion criteria are: (1) an already established diagnosis of dementia or a psychiatric disorder (according to DSM-IV) which could explain the behavior problems (2) MMSE-

score ≤ 18 (3) medical history including traumatic brain injury, mental retardation, drugs or alcohol abuse (4) lack of reliable informant (5) insufficient communicative skills of either patient or the closest informant (language, serious hearing impairment or behavioral disturbances including threatening or physical aggression) (6) acute onset of behavioral problems (7) clinically apparent aphasia or semantic dementia (8) MRI contraindications

Sample size

A total of 25 FTD patients is required to achieve a power of 79% when testing whether the sensitivity of MRI for detecting FTD is larger than 25% (using a one-sided exact test for a binomial proportion with p=0.05) under the alternative hypothesis that the sensitivity is 50%. A cohort size of 158 will yield the required number of FTD patients assuming a FTD prevalence of 27% and a drop-out percentage of 40% after two years of follow-up.
At this point we have included 102 patients.

Baseline procedure

After inclusion an informed consent is signed by the patient or, in case of incompetence of giving a fully informed consent, obtained from the caregiver or legal representative [16]. Reasons for exclusion or refusals of patients to participate in the LOF-study are registered as well as their age, gender, clinical diagnosis.

Demographic and examination variables are collected at baseline by means of a structured interview (table 1). Furthermore, all patients undergo a neuropsychological test battery, testing attention, concentration, memory, linguistic and visuospatial skills, with a special focus on executive functioning (planning, impulse regulation and mental flexibility) and theory of mind testing [17].

Neuro-imaging

All patients undergo a MRI-scan of the brain, acquired on a 3T Signa HDxt scanner (GE Medical Systems Milwaukee, WI) following a standard MRI protocol for dementia. The MRI-scans are visually assessed by an experienced neuroradiologist blinded to the patients' complaints and medical history by scanning all patients. Specific FTD features like mesio-frontal, orbito-frontal and temporal atrophy are described. Other MRI-parameters (medial temporal lobe atrophy, global cortical atrophy, posterior atrophy and white matter hyperintensities) are scored using appropriate scales [26-28]. In case of normal or insufficiently explanatory MRI-results (not explaining fronto-subcortical dysfunction) a [^{18}F]FDG-PET-scan is made on an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, USA). All PET-scans are rated and judged by a nuclear medicine physician blinded to the patients' complaints and medical history.

demographic variables	age, gender, level of education and (previous) occupation
symptoms according	cognitive and non-cognitive symptoms and main complaints according to patient and caregiver or spouse
neurological examination	physical examination, including structured examination of cognitive and frontal behavior disorders
medical history	vascular risk factors, psychiatric disorders, Parkinson's disease, amyotrophic lateral sclerosis, thyroid diseases, dyslexia, autism spectrum disorders, severe somatic disorders and traumatic or repetitive injury of the head
family history	data collection of first- and second-degree relatives on vascular risk factors, psychiatric disorders, Parkinson's disease, motor neuron disease, dyslexia and autism spectrum disorders
medication	all medications taken will be recorded
smoking and alcohol	previous and present smoking and alcohol intake measurements based on the interview with patient, caregiver and previous medical documentation
FBI	*Frontal Behavioral Inventory* [18-21]
SRI	*Stereotypy Rating Inventory* [22]
MADRS	*Montgomery Asberg Depression Rating Scale* [23]
MINI-International Neuropsychiatric Interview	Structured psychiatric interview using the DSM-IV criteria *Mini-International Neuropsychiatric Interview* [24]
PANSS	Measuring (the severity of) symptoms that could be caused by psychosis or schizophrenia using the *Positive and Negative Syndrome Scale* [25]
disease awareness and insight	awareness and insight using a visual analogue scale: patient and spouse both independently report the degree of change in behavior and character and the burden it causes on their live(s)

Table 1: Baseline variables from history and examination

CSF markers

CSF is obtained with a lumbar puncture that is performed according to a standard medical procedure in the lateral position in the L4-L5 or L5-S1 intervertebral space. CSF is collected in polypropylene tubes and centrifuged within an hour. The supernatant is stored in 0.5 cc aliquots at -80 ^{o}C degree Celsius. Laboratory analysis of levels of total-tau (T-tau), phosphorylated-tau (P-tau) and amyloid-β peptide concentrations take place using commercially available ELISA's (Innogenetics, Belgium) on a routine basis.

Genetic and pathological confirmation

As part of routine clinical workup, patients are referred for clinical genetic counselling and testing in any case of a positive family history for early onset dementia. Genetic screening for the most common mutations causing early-onset dementia include the MAPT, GRN, C9orf, PSEN1 and APP gene [4;5].

At baseline, patients are informed about the possibilities of brain bank donation via the Dutch brain Bank. Eventually, this may lead to pathological confirmation for a proportion of cases.

Diagnostic procedure

After the baseline assessment (table 1) both the neurologist and the psychiatrist determine the most likely diagnosis and their level of confidence (using a visual analogue scale) separately and blinded to the results of additional investigations. Diagnosis is based upon the NIA-AA guidelines for Alzheimer's disease, the NINDS-AIREN-criteria for vascular dementia, the international consensus diagnostic criteria for dementia with Lewy Bodies, the DSM-IV for psychiatric disorders and the International bvFTD Criteria Consortium (FTDC) [11;29-31]. Secondly, the neurologist as well as the psychiatrist reconsiders their previously stated diagnosis, taking the additional neuroimaging and CSF results into account. This is promptly followed by a multidisciplinary meeting, deciding the most likely diagnosis and composing a plan of treatment, psycho-education and/or guidance.

Follow-up procedure

After 1 year, the assessment summarized in table 1 takes place again, apart from the MINI-PLUS and neuropsychological examination. The clinical diagnosis and (therapeutical) management may be modified according to possible new clinical insights. Two years after the baseline assessment, clinical assessment is repeated as well as a neuropsychological examination and MRI, resulting in a prospective longitudinal follow-up. Dropout and loss to follow-up are described. The data collection at base-line and follow-up is summarized in figure 1.

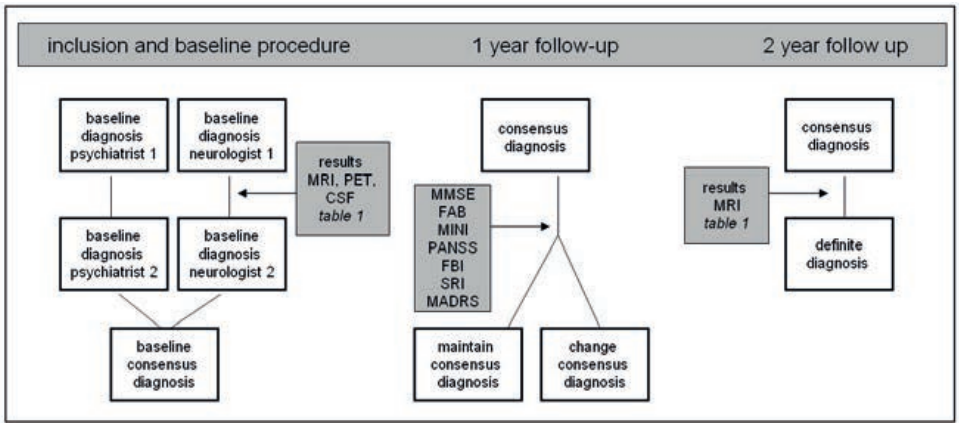

Figure 1: Timeline patients LOF-study from inclusion until definite diagnosis

Data analysis

Differences in baseline characteristics between the groups (bvFTD vs. non-bvFTD) are analyzed using χ^2- and T-tests as appropriate.

Diagnosis is determined in a multidisciplinary consensus meeting at baseline. Receiver operator characteristic (ROC) curves are used to evaluate the diagnostic values of baseline assessment-tests, CSF-analysis and imaging for a bvFTD diagnosis. Areas under the curve are investigated. Sensitivity, specificity, positive and negative predictive values for the optimal cut-off points are calculated. After two years of follow-up a more accurate diagnosis is made, as the presence or absence of disease progression is taken into account. Baseline assessment-tests, CSF-analysis and neuro-imaging will be compared with the diagnosis of bvFTD at follow-up using ROC curves. Additionally, the optimal set of diagnostic tests will be determined using logistic regression models and ROC curves.

Characteristics of dropouts and losses to follow-up will be described.

Outcome measures

The final multidisciplinary diagnosis after 2 years of follow-up is considered as the 'silver' diagnostic standard, whereas a diagnostic golden standard is reserved for either genetic or pathological confirmation of the diagnosis.

In the cross-sectional analyses, the multidisciplinary diagnosis at baseline is the used standard and outcome measures are (1) the distribution of various diagnoses underlying a late-onset frontal lobe syndrome, (2) the (non-)discrepancy between the neurologists' and psychiatrists' diagnosis and their influence on the multidisciplinary diagnosis and (3) the additional value (sensitivity and specificity) of neuroimaging and CSF results over the clinical information in patients with LOF.

In the longitudinal analyses after the 2-year follow-up period, the main outcome measures are (1) the sensitivity, specificity, positive and negative predictive values of MRI, [^{18}F]FDG-PET and CSF biomarkers for bvFTD, (2) the predictive value of patterns of frontal lobe dysfunction for the eventual clinical diagnosis.

Ethical considerations

The study has been approved by the Medical Ethical Committee of the VU medical center Amsterdam.

DISCUSSION

This paper describes the LOF-study (Late Onset Frontal lobe syndrome study), an ongoing naturalistic cross-sectional and prospective follow-up study on the etiology of late onset frontal lobe syndrome, released in April 2011. This study also investigates the role of MRI,

PET and CSF-data in distinguishing and predicting the different underlying pathologies with a special focus on bvFTD on the one hand and psychiatric disorders on the other. The sensitivity, specificity, positive and negative predictive value of laboratory and imaging results are being measured.

This study holds several strengths. This is the first multi-center study integrating neurological and psychiatric diagnostic work-up and follow-up in patients with a late-onset behavioral disorder and the study cohort to be achieved is relatively large. This might enable us to build a new paradigm for the early diagnosis of bvFTD. Moreover, this approach may yield reduction of diagnostic delay on both sides of the diagnostic spectrum. The inclusion based on symptoms instead of established diagnosis provides an unbiased setting, approaching the clinical practice as much as possible.

There are a few challenges in this study. Some patients with more severe disorders must be excluded because of their extreme behavioral disorder. Since the MMSE is widely known it is used to exclude patients with severe cognitive impairment (<18) although it is a global assessment scale. Furthermore, because participants are recruited in an academic medical center, inclusion bias may exist resulting in a relatively complex cohort. Another limitation is that pathological verification of the clinical diagnosis will only take place in a small proportion of cases.

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