Building a New Paradigm for the Early Recognition of Behavioral Variant Frontotemporal Dementia: Late Onset Frontal Lobe Syndrome Study

Welmoed A. Krudop, M.D.,
Cora J. Kerssens, M.D.,
Annemieke Dols, M.D., Ph.D.,
Niels D. Prins, M.D., Ph.D.,
Christiane Möller, M.Sc.,
Sigfried Schouws, Ph.D.,
Frederik Barkhof, M.D., Ph.D.,
Bart N.M. van Berckel, M.D., Ph.D.,
Charlotte E. Teunissen, Ph.D.,
Wiesje M. van der Flier, Ph.D.,
Philip Scheltens, M.D., Ph.D.,
Max L. Stek, M.D., Ph.D.,
Yolande A.L. Pijnenburg, M.D., Ph.D.

Objective: *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]-fluorodeoxyglucose-positron emission tomography (FDG-PET), and cerebrospinal fluid (CSF) biomarkers in predicting and identifying the different underlying pathologies with a special focus on the behavioral variant of frontotemporal dementia.* **Methods:** *The LOF study is an observational cross-sectional and prospective follow-up study. Patients aged 45–75 years with a frontal behavioral change consisting of apathy, disinhibition, or compulsive/stereotypical behavior were included (April 2011–2013). Patients underwent a multidisciplinary assessment by a neurologist and psychiatrist and MRI, CSF, and PET measurements at inclusion and after 2 years of follow-up.* **Results:** *The diagnostic added value of MRI, PET, and CSF results and their predictive value will be measured after 2 years of follow-up.* **Conclusion:** *This is the first large-scale prospective follow-up study of patients with late-onset behavioral disorders.* (Am J Geriatr Psychiatry 2013; ■:■–■)

Key Words: bvFTD, early diagnosis, psychiatry, 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 the behavioral variant of frontotemporal dementia (bvFTD), psychiatric disorders like depression or schizophrenia, or other types of dementia, may present with an LOF.[1] The main form of dementia presenting with an 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 between ages 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]

Received April 2, 2012; revised December 12, 2012; accepted December 31, 2012. From the Alzheimer Centre and Department of Neurology (WAK, NDP, CM, WMvdF, PS, YALP), Department of Radiology (FB), Department of Nuclear Medicine & PET Research (BNMvB), and Neurological Laboratory, Department of Clinical Chemistry (CET), VU University Medical Centre, Amsterdam, the Netherlands; and Department of Old Age Psychiatry (CJK, AD, SS, MLS), GGZInGeest, Amsterdam, the Netherlands. Send correspondence and reprint request to Welmoed A. Krudop, M.D., Alzheimer Centre and Department of Neurology, VU University Medical Centre, De Boelelaan 1117, 1081 HV Amsterdam, 1007 MB, Amsterdam, The Netherlands. e-mail: w.krudop@vumc.nl

Supplemental digital content is available for this article in the HTML and PDF versions of this article on the journal's Web site (www.ajgponline.org).

http://dx.doi.org/10.1016/j.jagp.2013.02.002

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, dementia with Lewy bodies, and vascular dementia, 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 established new diagnostic criteria, because 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 five of the six 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 cerebrospinal fluid (CSF) results could improve diagnosis of bvFTD; however, the added value of these biomarkers remains to be established.

Magnetic resonance imaging (MRI) 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-positron emission tomography (PET) with visual rating of the glucose analog, sensitivity rises to a range from 81% to 90%.[12] However, specificity of these methods is limited, because structural and 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. However, 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.

This article provides a description of the Late Onset Frontal Lobe Syndrome study (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 is an ongoing multicenter observational, cross-sectional, and prospective follow-up study. Patients are recruited through the memory clinic of the Alzheimer Centre of the VU Medical Centre and the Department of Old Age Psychiatry of the GGZInGeest (inpatients and outpatients), Amsterdam, the Netherlands, between April 2011 and June 2013.

Definition of the LOF

LOF is defined as behavioral changes 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 years, with symptom onset between the ages of 40 and 70 and (2) Frontal Behaviour Inventory score of 11 or higher and/or a Stereotypy Rating Inventory score of 10 or higher. Exclusion criteria are as follows: (1) an already established diagnosis of dementia or a psychiatric disorder (according to the *Diagnostic and*