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Diagnostic instability over time in the late-onset frontal lobe syndrome: When can we say it's FTD?

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Highlights de Boer et al., 2022

What is the primary question addressed by this study?

We investigated diagnostic instability over time of patients with a late-onset behavioural disorder included in a neuropsychiatric cohort and identified clinical hallmarks that contribute to diagnostic instability.

What is the main finding of this study?

Between baseline and the 2 year follow-up visit 21.2% of all patients diagnosed with frontotemporal dementia, primary psychiatric disorders or other neurological disorders switched diagnosis. After the 2-year follow-up only 5.8% of all patients switched diagnosis. Clinical characteristics contribute to diagnostic instability were identified.

What is the meaning of the finding?

A bvFTD diagnosis remains stable enough to say a patient with late-life behavioral disorder has bvFTD if our clinical lessons are taken into consideration.

Diagnostic instability over time in the late-onset frontal lobe syndrome: When can we say itôs FTD?

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Abstract [250/250]

Objectives

Distinguishing sporadic behavioural variant of Frontotemporal Dementia (bvFTD) from late-onset primary psychiatric disorders (PPD) remains challenging with the lack of robust biomarkers. An early bvFTD misdiagnosis in PPD cases and vice-versa is common. Little is known about diagnostic (in)stability over longer period of time. We investigated diagnostic instability in a neuropsychiatric cohort up to 8 years after baseline visit and identified which clinical hallmarks contribute to diagnostic instability.

Design

Diagnoses of participants of the Late-Onset Frontal lobe (LOF) study were collected from the baseline visit (T0) and the 2-year follow up visit (T2). Clinical outcomes were retrieved 5 to 8 years after baseline visit (T_{final}). Endpoint diagnoses were categorized into bvFTD, PPD and Other Neurological Disorders (OND). We calculated the total amount of participants that switched diagnosis between T0-T2 and T2-T_{final}. Clinical records of participants that switched diagnosis were assessed.

Results

Of the 137 patients that were included in the study, the final diagnoses at T_{final} were bvFTD 24.1% (n=33), PPD 39.4% (n=54), OND 33.6% (n=46) and unknown 2.9% (n=4). Between T0-T2, a total of 29 (21.2%) patients switched diagnosis. Between T2-T_{final}, 8 (5.8%) patients switched diagnosis. Prolonged follow-up identified few cases with diagnostic instability. Major contributors to diagnostic instability where a non-converting diagnosis of possible bvFTD and a probable bvFTD diagnosis based on informant-based history and abnormal FDG-PET scan whilst having a normal MRI.

Conclusion

Considering these lessons, a FTD diagnosis remains stable enough to conclude that two years is sufficient to say if a patient with late-life behavioural disorder has FTD.

Keywords: frontotemporal dementia, primary psychiatric disorder, neurodegeneration.

INTRODUCTION

The behavioural variant of frontotemporal dementia (FTD) is the most prevalent form of FTD and is associated with progressive degeneration of the frontal lobes, anterior temporal lobes, or both [1, 2]. Neuropsychiatric symptoms overshadow the cognitive disabilities, especially in the early disease phase [3-6] and at an earlier age of onset [7]. Alterations in social cognition often represent the earliest and core symptoms of behavioural variant of FTD (bvFTD), resulting in emotional disengagement and socially inappropriate responses or activities [8-10]. Apathy, inertia, disinhibition, loss of empathy or stereotyped, compulsive behaviours are common clinical features in bvFTD. Consequently, due to this heterogeneous and often predominantly behavioural clinical presentation, both other neurodegenerative diseases as well as various psychiatric disorders are crucial to consider as a differential diagnosis [6].

A bvFTD diagnosis is made following the clinical consensus criteria developed by an international expert group [4]. A *possible* bvFTD is a merely syndromic, mainly behavioural, diagnosis, while a *probable* bvFTD is supported by imaging findings. A *definite* bvFTD diagnosis is made if pathological confirmed or if a causal FTD mutation is present, the latter also known as genetic FTD. The deficits and behavioural disturbances should not be accounted for by non-neurodegenerative diseases and/or a psychiatric diagnosis in order to accurately diagnose bvFTD.

However, discerning non-genetic, or sporadic, bvFTD from a heterogeneous neuropsychiatric population later in life remains challenging, particularly since robust biomarkers for sporadic bvFTD and PPD are lacking. This challenge is illustrated by the high percentages reported, ranging from 50% to 71%, of initial psychiatric diagnoses in bvFTD [11-13] and a delay of 6 years to diagnose bvFTD [14]. We have previously shown that a bvFTD diagnosis is unstable within a follow-up period of two years in the Late Onset Frontal Lobe (LOF) study, with 49% of bvFTD patients switching diagnosis [15]. This instability has major impact on patients and their family as misdiagnosis of PPD in bvFTD and vice versa delays adequate treatment and/or correct information of the disease and prognosis.

As a response to this diagnostic challenge, the Neuropsychiatric International Consortium of Frontotemporal Dementia (NIC-FTD) has established clinical recommendations to distinguish bvFTD from PPD [16]. These recommendations include clinical and neuroimaging follow-up in diagnostic ambiguous cases. The duration of this follow-up in order to achieve diagnostic precision remain elusive and little is known about the diagnostic (in)stability after two years of follow-up in a neuropsychiatric cohort.

The aim of the present study was to investigate diagnostic instability of patients with a late-onset behavioural disorder from the LOF study. Second, we aimed to identify clinical hallmarks that contribute to diagnostic instability.

Methods

Patients

Subjects included participants of the LOF study. The LOF study is an observational study that included subjects with behavioural changes with onset between the ages of 45 and 75 years. Participants were recruited and followed-up in the memory clinic of the Alzheimer Centre Amsterdam and the out-patient clinic of psychiatry of the GGZInGeest, Amsterdam, The Netherlands, between 2011 and 2015. Demographics and examination variables, including a neuropsychological examination, imaging, genetic screening were collected at baseline. Following standard diagnostic work-up, cerebrospinal fluid (CSF) was collected at the memory clinic for n=107 subjects before enrolment in the LOF-study to screen for the presence of AD-biomarkers [17]. Two years after baseline (T2), the LOF-study participants were invited to return to the outpatient clinic for a re-assessment, similarto the baseline visit. The LOF-study followed clinical criteria of the National Institute on Aging-Alzheimer's Association guidelines for Alzheimer disease, the International Consensus Diagnostic Criteria for dementia with Lewy bodies, the Diagnostic and Statistical Manual of Mental Disorders the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherch® et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia and the International bvFTD Criteria Consortium [4, 18-20]. With adherence to DSM-IV, órelational problemsôin this study were defined as ña pattern of interaction between spouses or partners characterized by negative communication (e.g., criticisms), distorted communication (e.g., unrealistic expectations), or noncommunication (e.g., withdrawal) that is associated with clinically significant impairmentò. A total of n=112 (81.7%) participants completed the T2 visit in the clinic.

Specific inclusion and exclusion criteria, clinical assessment, imaging protocol, diagnostic procedure at baseline and informed consent procedure have been described previously [21].

Diagnoses T_{final}

Five to eight years after baseline visit (T_{final}), the clinical outcome final diagnosis of the patient was retrieved. Of the initial 137 LOF-study participants, n=52 (38.0%) subjects still received clinical follow-up at the memory clinic of the Alzheimercentrum Amsterdam. For the remaining n=85 cases, the clinical outcome was retrieved by either contacting their general practitioner or psychiatrist/neurologist/geriatrist or other medical specialist. The general practitioner in the Netherlands receives written correspondence on all patientôs visits to medical specialists for diagnostics, therapies and/or hospital admissions. Patients were lost

to follow up when they refused follow-up or when the patient died while diagnosis remained uncertain or unknown. With this T_{final} method we were able to collect follow-up for n=25 LOF-study participants that were not seen at the 2-year follow-up visit of the LOF-study but did have information available around the anticipated 2-year follow-up visit that was adequate to come to a diagnosis. This led to retrieving diagnoses for n=9 cases at the time of the T2 visit (Figure 1).ôThe (retrieved) diagnoses were grouped into ódvFTDô, ófPPDôand óother neurological disorders (OND)ô

Clinical measurements

At baseline of the LOF-study, demographic variables and clinical measurements including Mini-mental State exam (MMSE), Montgomery Asberg Depression Rating Scale (MADRS), Frontal Assessment Battery (FAB), Frontal Behavioral Inventory (FBI) and Stereotypical Rating Inventory (SRI), neuropsychological executive dysfunction determined by translating z-scores to a dichotomous variable and the Ekman faces test were determined for all participants as previously described [21, 22]. The presence of typical FTD like atrophy patterns in MRI and frontotemporal (FT) hypometabolism in FDG-PET were assessed by visual inspection by a trained neurologist as described in the study of Vijverberg *et al.,* 2016 [23]. The baseline measurements were compared between the endpoint (T_{final}) diagnostic groups.

Genetic testing in LOF study

All participants, regardless of baseline diagnosis or family history, were screened for the length of the repeat expansion in the chromosome 9 open reading frame 72 (*C9orf72*) since bvFTD caused by a *C9orf72* repeat expansion can often debut with psychiatric symptoms [24] such as late-onset psychosis and/or bipolar disorder [25]. Participants with a positive family history for dementia were also screened for the presence of a mutation in the microtubule associated protein tau (*MAPT*) and progranulin (*GRN*).

Statistics

IBM SPSS Statistics for Windows was used to perform statistical analyses, version 24. The baseline characteristics were compared between the final three diagnostic groups. Normally distributed continuous values were compared between diagnostic groups using a one way ANOVA, and Bonferonni as post hoc test. Continuous values without a normal distribution were examined using a Kruskall Wallis and post-hoc Mann Whitney U tests. Results were considered to be statistically significant if $p < 0.05$, except for the results from the Mann Whitney U test being performed after the Kruskal Wallis test ($p < 0.05$ / three diagnostic groups, $p < 0.017$). Pearsonôs X2-test was used when dichotomous variables were

compared. For between-group comparisons with Ò5 observations, a Fisherôs Exact test was performed. Figures were made using R studio (version 4.0.3, R Development Core team 2010).

Ethical considerations

The study was approved by the Medical Ethical Committee of the AmsterdamUMC, location VUmc, Amsterdam.

Results

Five to eight years after baseline visit, the final diagnoses were the following for the 137 patients; bvFTD 24.1% (n=33), PPD 39.4% (n=54), OND 33.6% (n=46) and unknown 2.9% (n=4) (see Table 1). Most bvFTD patients were sporadic, with only three bvFTD patients (2.2%) carrying a genetic mutation *(C9orf72* n=2, *GRN* mutation n=1).

Diagnostic instability T0-T2

Between the baseline and T2 visit, a total of 29 (21.2%) patients switched diagnoses. Twelve patients from the bvFTD group switched to the PPD group, of which six patients were initially diagnosed with possible bvFTD and six with probable bvFTD. Six patients switched from a bvFTD to a OND diagnosis. Of the baseline PPD group, one patient switched to bvFTD and seven patients switched to the OND group. Of the baseline OND group, three patients switched to the PPD group. Sixteen patients were lost to follow up at T2. Resulting in a total of 29 patients in the bvFTD group, 54 in the PPD group and 38 patients in the OND group at T2.

Diagnostic instability T2-T_{final}

Between T2 and T_{final}, a total of eight (5.8%) patients switched diagnosis. In the bvFTD group, two patients switched to PPD and two switched to OND. In the PPD group, two patients switched to bvFTD and two patients switched to OND. From the OND group, no patients switched diagnosis after T2 (Figure 2). The clinical characteristics of the patients that switched between T0 and T2 and between T2 and T_{final} are shown in Table 3.

Baseline clinical and demographical characteristics

The baseline demographics and clinical examination of the patients in each final diagnosis group (T_{final}) are shown in Table 2. The age at presentation (ANOVA, $F(2, 132)= 7.03$, $p<0.01$), prevalence of positive psychiatric history (χ^2 (1, N=133)= 8.94, p=0.01), the SRI score ($H(2)=17.36$ $p<0.001$), MADRS score ($H(2)=11.45$ $p<0.01$), Ekman Faces test score

(ANOVA, F(2, 103)=9.97, p<0.001), the presence of FT on the MRI scan (ɢ2 (1, N=133)=51.33, p<0.001) and the presence of FT hypometabolism on the FDG-PET scan (ɢ2 (1, N=87)=37.83, p<0.001). differed significantly between the bvFTD, PPD and OND group. Post-hoc comparison showed that the PPD were significantly younger than bvFTD (mean æ 3.7 years, SD=1.46, p=0.04) and OND (mean æ4.7 years, SD=1.33, p<0.01). There was no significant difference in age at presentation between bvFTD and OND (mean æ1.3 years, SD=1.51, p=1.00). There was a higher prevalence of positive psychiatric history in the PPD group (51.9%) compared to the bvFTD group (24,0%, ɢ2 (1, N=87)=6.4, p=0.01) and compared to the OND group (28.3%, ɢ2(1, N=100)=5.72, p=0.02).

The SRI score was higher in the bvFTD group (median 9.5) compared to the PPD group (median 4, z=-3,15, p<0.01) and to the OND group (median 1.5, z=-4.00, p<0.01). There was no significant difference in SRI score between the PPD and OND group (z=-1,37, p=0.17). The PPD group had a higher MADRS score (median 12.5) compared to the bvFTD group (median 6.5, z=-3.06 p<0.01) and to the OND group (median 6.5, z=-2.55, p=0.01). There was no difference in MADRS score between the bvFTD and OND group (z=-0.83, p=0.41). Bonferroni post-hoc comparison showed that the bvFTD group has a lower score on the Ekman Faces test compared to the PPD group (mean æ9.35 points, SD=2.10, p<0.001) and to the OND group (mean æ6.62 points, SD=2.16, p<0.01). No significant differences were found in the Ekman Faces test between the PPD and OND group (mean æ2.73 points, SD=1.88, p=0.45).

Comparing the presence of FTD like atrophy on the MRI scan between each groups showed a higher prevalence of FTD like atrophy in the bvFTD group (63.6%) compared to the PPD group (3.7%, Fisherôs Exact test, N=87), p<0.001) and compared to the OND group (8.7%, Fisherôs Exact test, N=79, p<0.001). This significant difference in presence of FT atrophy on the MRI scan was not seen between PPD and OND (Fisherôs Exact test, N=100, p=0.41). Likewise, the bvFTD group showed a higher prevalence of FT hypometabolism (93.3%) compared to the PPD group (30.2%, Fisherôs Exact test, N=59, p<0.001) and to the OND group (22.6%, Fisherôs Exact test, N=47 p<0.001). This difference was not seen between the PPD and OND group (ɢ2, (1, N=74)=0.54, p=0.47).
No significant group differences between the three groups bvFTD, PPD and OND were found for sex (ɢ2 (1, N=133) =5.84, p=0.05), education level (H(2)= 3.70, p=0.16), disease duration (H(2)= 0.83, p= 0.66), FBI (ANOVA, F(2, 130)=0.49, p=0.61), MMSE (H(2)= 1.34, p= 0.51), FAB (H(2)= 5.91 p= 0.05) and presence of executive dysfunction at neuropsychological examination (ɢ2 (1, N=133)=0.19, p=0.91).

Clinical hallmarks of patients that switched diagnosis

Between T0 and T2, a total of 29 (21.2%) patients switched diagnosis, and 8 cases (5.8%) switching diagnosis after T2. It is clinically relevant to describe the clinical hallmarks from cases that switched diagnosis to identify clinical characteristics of patient that are of risk misdiagnosis . We therefore carefully examined the clinical records of these patients (Figure 3 and 4). We identified three main clinical hallmarks or pitfalls that contributed to diagnostic instability, including;

i) No MRI of the brain was repeated after two years when the first MRI was not conclusive or non-supporting for bvFTD;
ii) A patient meeting clinical Rascovsky criteria only on informant-based history whilst meeting a probable bvFTD diagnosis based on an abnormal FDG-PET scan alone in the presence of a normal MRI;
iii) A diagnosis of possible bvFTD without disease progression at 2 years of follow-up was endured.

DISCUSSION

This study aimed to investigate diagnostic (in)stability over time of the LOF study and which clinical characteristics contribute to this (in)stability. This investigation can guide clinicians that are in diagnostic doubt when assessing patients with late onset behavioural changes suspect for bvFTD, PPD or OND, when to say it is FTD. Between baseline and the 2 year follow-up visit, 29 (21.2%) patients switched diagnosis. After the 2 years, fewer patients switched diagnosis (5.8%).

Multiple clinical lessons can be learned from carefully examining the cases that switched diagnosis. First, a possible bvFTD diagnosis without clinical progression after 2 years is most likely to switch diagnosis. If genetic testing is negative and the MRI scan is clear of atrophy or vascular lesions, a possible bvFTD diagnosis is probably a reference to the phenocopy syndrome of bvFTD [26, 27] or an underlying psychiatric disorder. This warrants clinicians to consider a possible bvFTD diagnosis only as differential diagnosis and to monitor the patient closely before making a false, life changing diagnosis that can withhold adequate psychiatric treatment. Second, we found that an informant-based history can point strongly to meet all clinical bvFTD criteria but that in case of inconclusive neuroimaging results it is necessary to ask an additional informant (preferably from outside the family) for information about symptom progression over time. Third, when a patient has late-onset behavioural changes with frontal or temporal brain atrophy on the MRI within two years of follow up but the patient does not fulfil enough bvFTD criteria: it is very likely that the patient will develop probable

bvFTD over time. Likewise, if a patient fulfils the bvFTD criteria but imaging only shows subtle frontal or temporal atrophy, a repeated MRI after two years gives clearance: if there is (mild) progression of subtle atrophy it seems very likely that probable bvFTD is the case. These clinical lessons that could be concluded from this study, are in line with the clinical recommendations to distinguish bvFTD from psychiatric disorders by the NIC-FTD consortium. Among those are the recommendations to include social cognition tests in the neuropsychological testing for bvFTD, the implementation of a standardized review protocol of a brain MRI with validated visual atrophy rating scales and to mainly use a FDG-PET for excluding bvFTD [16, 28]. In retrospect, if these clinical recommendations were available at the time and taken into account at baseline, together with our clinical lessons, the diagnostic switches after two year of follow-up could have been prevented. Noteworthy, in our study, the Ekman Faces test was included as social cognition test in neuropsychological examination at baseline, which on a group level, showed that the bvFTD group has a lower score on the Ekman Faces test compared to the PPD group and to the OND group. Likewise, previous work from our group has shown that the Ekman-60 can be successful in differentiating between bvFTD and other neurodegenerative disorders and psychiatric diseases [22]. Yet, all twelve patients that switched from bvFTD to PPD between T0 and T2 scored below the cut-off of 46/60 points on the Ekman Faces test. This supports the importance to include social cognitive tasks in the diagnosis of bvFTD but also emphasizes the need of a specific social cognition test or combination of tests that can accurately distinguish bvFTD from PPD and OND [29]. Of importance, the NIC-FTD consortium recommend in 2020 using Neurofilament light (NfL) serum or CSF levels to help distinguish between PPD and neurodegenerative disorders such as FTD. Unfortunately, there were no NfL levels clinically available at the time of the LOF-study and these could not be taken into consideration by the clinicians.

The comparison of the characteristics, demographics and clinical, neuropsychological and neuroimaging examinations measured at baseline between the endpoint (T_{final}) diagnostic groups (bvFTD, PPD and OND) were in agreement with previous analysis when the diagnostic groups, determined at T2 of the LOF study, were compared [22, 30].

As limitation, this study had significant delays due to the implemented General Data Protection Regulation in May 2018 which resulted in a change in methods to retrieve the data from the general practitioner or current seen specialist. Furthermore, the majority of the LOF participants were not clinically assessed in the memory clinic at T_{final}. In these cases, a general consensus final diagnosis was made after retrieving available current medical information from the general practitioner or current seen specialist. In addition, our study

methods withheld us from investigating the effects of different treatment or different social support systems between diagnostic groups that could have influenced the clinical picture at time of the follow-up visits. Moreover, our study took place in a tertiary memory clinic. It is conceivable that bvFTD patients were referred in a later disease stage. This is supported by the median disease duration before visiting the memory clinic of 3 years for the PPD and OND group and 3.5 for the FTD group. This can have implications for the clinical examinations (e.g. neuropsychological testing and brain imaging) and information of the disease course of LOF participants already being available at baseline. Eventually, this could have influenced the differential diagnoses and diagnostic accuracy of the clinician. Nevertheless, this empathizes that the 21.2% cases that switched diagnoses within 2 years after the baseline visit might be even higher in a non-tertiary memory clinic. As final limitation, it is debatable whether the diagnosis relational problems are correctly assigned to be part of the primary psychiatric disorder group. In retrospect, it is possible that these cases would have been diagnosed with the phenocopy syndrome of bvFTD based on current available literature. Although the combination of relational problems with recent life events and cluster C personality traits seem to be possible underlying psychiatric or psychological condition, an evident psychiatric disorder as cause for this phenocopy syndrome has not yet been identified (Gossink et al., 2016).

We showed that after two years of follow up a FTD diagnosis remains stable enough to conclude that two years is sufficient to say a patient with late-life behavioural disorder has FTD on the condition that our clinical lessons are taken into consideration.

Authors contribution

Sterre C.M. de Boer, MD, contributed to study design, data collection, data analysis, interpretation, and manuscript writing.
Flora Gossink, MD, Ph.D., contributed to contributed to study design, data collection, interpretation, and manuscript writing.
Welmoed Krudop, MD, Ph.D., contributed to contributed to study design, data collection, interpretation, and manuscript writing.
Everard Vijverberg, MD, Ph.D., contributed to data analysis and interpretation.
Sigfried Schouws, MD, Ph.D., contributed to data collection, and revision of manuscript for intellectual content.
Lianne Maria Reus, Ph.D., contributed to data collection, interpretation and manuscript writing.
Yolande A.L. Pijnenburg, MD, Ph.D., contributed to study design, data collection, interpretation, and manuscript writing.

Annemiek Dols, MD, Ph.D., contributed to study design, conceptualization, data interpretation, and manuscript writing.

Conflicts of Interest and Source of Funding

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Data Statement:

Yes. AAIC 2022 in San Diego at the ISTAART-PIA day.

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Figure Legend:

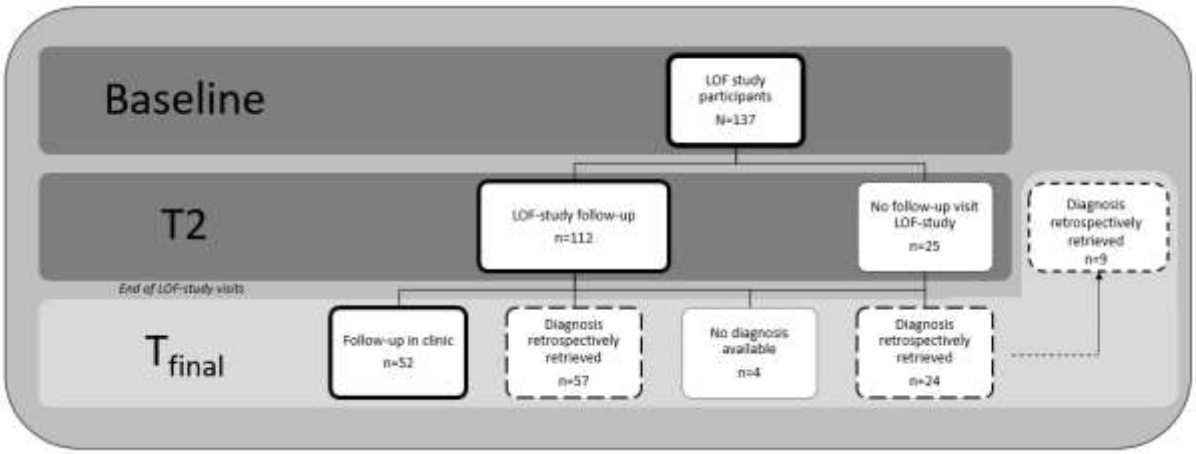

Figure 1. Flowchart of the LOF-study visits, clinical follow-up and retrospective diagnosis retrieval.
Dark grey: LOF-study. Light grey: retrieval clinical outcome current study.
Abbrevations: LOF-study: Late-Onset Frontal lobe study. T2: study follow-up LOF study 2 years after baseline visit. T_{final}: clinical outcome 5-8 years after baseline visit of the LOF-study.

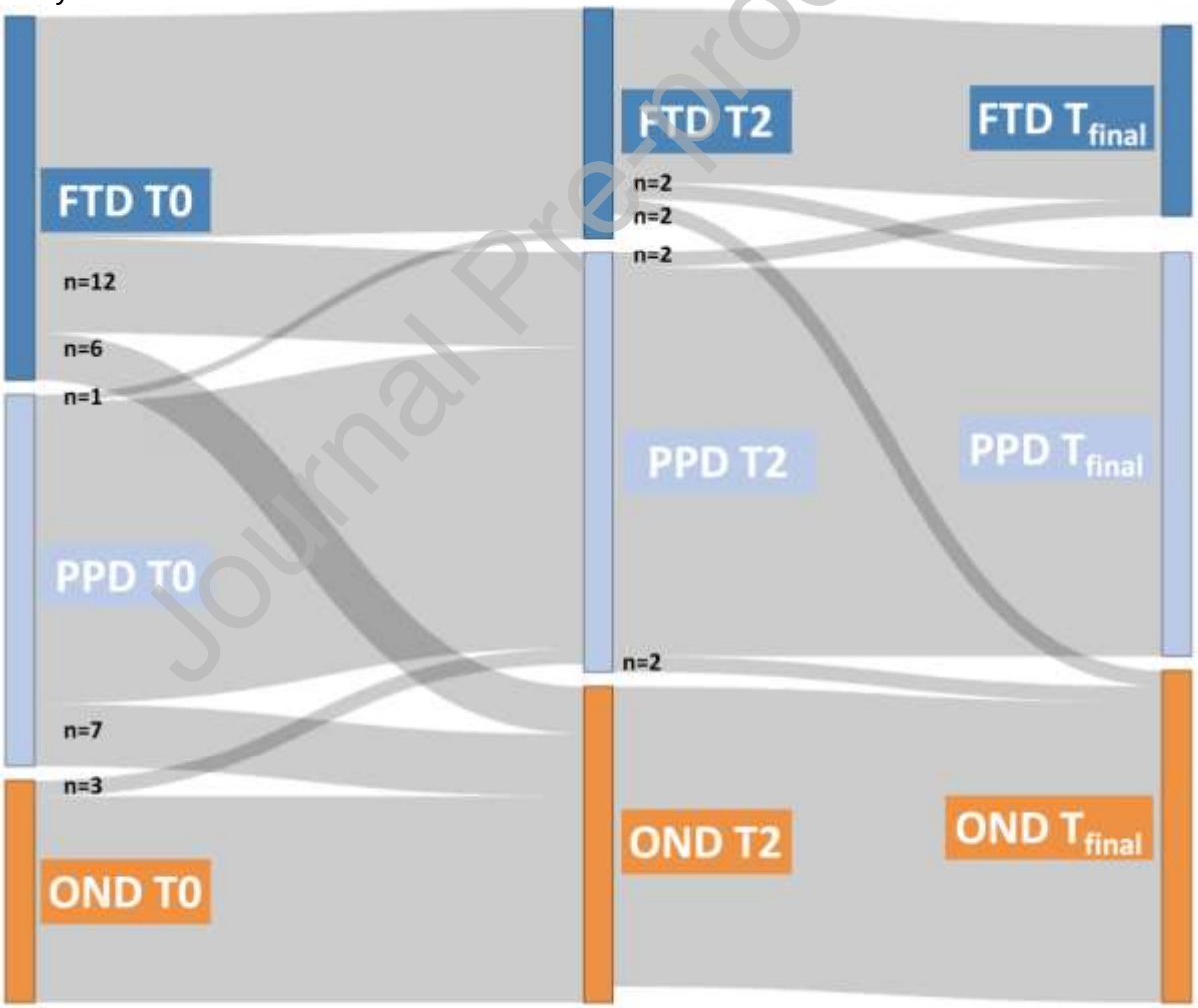

Figure 2. Patients that switched diagnosis between T0 and T2 and T2 and $T_{final.}$
T0: bvFTD n=45, PPD n=51, OND n=31 and unknown n=0.
T2: bvFTD n=29, PPD n=54, OND n=38 and unknown n=16.
Tfinal: bvFTD n=33, PPD n=54, OND n=46 and unknown n=4.
Abbreviations: FTD= frontotemporal dementia, PPD= primary psychiatric disorders, OND= other neurological disorders. T0= baseline visit, T2= follow-up visit 2 years after baseline, T_{final}= 5-8 years after baseline visit.

Figure 3. Case vignettes of patients that switched diagnosis between T0 and T2.

i. *Six patients switched from probable bvFTD to PPD.*
Four patients were diagnosed with a mood disorder and two with relationship problems. All six patients had a FDG-PET result supportive of bvFTD, only one patient also had an abnormal MRI. At baseline, in four out of these six 'converting' patients the neurologist and psychiatrist were convinced of a probable bvFTD diagnosis on the basis of a combination of 'clinical impression', a supportive informant based history and FDG-PET results supportive for a bvFTD diagnosis. The only patient having both an abnormal MRI and FDG-PET, was diagnosed with relationship problems. The bvFTD diagnosis was mainly based at an informant based history in combination with mild bifrontal brain atrophy. In all 6 patients the score at the Ekman Faces test was below a cut of score of 46. In three patients, there was the relatively high score of the SRI (>10). Remarkably, none of these six patients had a neuropsychological profile supportive for a bvFTD diagnosis, despite mild executive problems in two patients. In retrospect, this combination of a non-supportive neuropsychological test with only mild atrophy warrants clinicians to be cautious giving a diagnosis of probable bvFTD.

ii. *One patient switched from PPD to possible bvFTD*
At baseline this patient was diagnosed with a major depression with psychotic features even though she fulfilled the clinical criteria of possible bvFTD. After two years of follow up the behavioural problems (mainly apathy) turned out to be progressive which led to a diagnosis of possible bvFTD. This patient switched back to a PPD diagnosis after two years (see patient B, Figure 3)

iii. *Six patients switched from probable bvFTD to OND.*
Three patients were diagnosed with other FTD spectrum diseases, two patients with semantic dementia (SD) and one with cortical basal syndrome (CBS). During follow-up the behavioural problems were less pronounced than the semantic deficits in the SD patients. Likewise, in CBS patients the behavioural disorders were less pronounced than the bradykinesia and apraxia. The other three patient fulfilled the Rascovsky criteria for bvFTD, but all three required additional examination to rule out the second differential diagnosis that was given: one patient switched diagnosis to multiple sclerosis (MS) after an additional MS-protocol MRI scan gave confirmation of MS-like lesions at the baseline MRI scan. One patient switched to Parkinson's disease dementia after confirmation of a DAT-SPECT scan. One patient switched to the diagnosis of post-anoxic encephalopathy after a non-progressive second MRI and an observation at the psychiatric ward during follow-up was not suspect for bvFTD.

iv. *Seven patients switched from PPD to OND.*
Four patients switched from major depression disorder to other neurological disorders. One of these patients suffered from depression but over time autonomic dysfunction and movement disorder became more pronounced and the diagnosis switched to Multiple System Atrophy. Two of these patients switched to other dementia types (vascular dementia and progressive supranuclear palsy). The fourth major depression patient at baseline suffered from a depression that was almost completely in remission before he got a cardiac arrest close to the T2 visit after which he developed a cognitive disorder that was believed to be caused by a post-anoxic encephalopathy.
One patient switched from a diagnosis of autism spectrum disorder to DLB. At baseline, this patient already showed symptoms of DLB such as REM sleep behavior disorder and mild rigidity but did not fulfill DLB criteria until his follow-up visit.
One patient suffered from post-traumatic stress disorder and late onset behavioural changes that were caused by recent life changing events. The MRI at baseline showed mild vascular damage but this was not believed to be causally related to the presented symptoms. At follow-up, this patient developed progressive cognitive impairment and the MRI showed progression of the vascular lesions, causing the neurologist to switch diagnosis to vascular dementia. Likewise, the seventh patient changed diagnosis from subjective cognitive decline, possibly caused by mild mood problems, to vascular dementia after objectifying progression of memory symptoms and vascular lesions on the MRI scan.

v. *Three patients switched from OND to PPD.*
One patient was diagnosed with vascular mild cognitive impairment (VCI) due to a small thalamic ischemic lesion at baseline but changed diagnosis to an unclear psychiatric mood disorder and subjective cognitive complaints that did not correlate with the ischemic lesion. One patient with auditory hallucinations and atypical behavioural symptoms was diagnosed with dementia with Lewy body (DLB) at baseline but switched diagnosis due to a non-supportive DAT-SPECT scan at follow-up. The patient was re-evaluated by a psychiatrist and neurologist and was diagnosed with bipolar disorder.
The third patient was suffering from cognitive impairment, anxiety and behavioural change and was diagnosed with dementia due to obstructive sleep apnea syndrome (OSAS). The OSAS was successfully treated during follow-up. However, the symptoms did not improve and at the follow-up visit he was diagnosed with an anxiety disorder.

Figure 3. Case vignettes of patients that switched diagnosis between T0 and T2.

Figure 4. Case vignettes of patients that switched diagnosis between T2 and Tfinal.

Table 1. Diagnoses at baseline and final diagnosis (T_{final}).
Abbreviations: bvFTD = behavioural variant Frontotemporal Dementia; FTD-ALS = Frontotemporal Dementia-Amyotrophic lateral sclerosis; *C9orf7*2 expansion = Chromosome 9 open reading frame 72 repeat expansion; *GRN* = progranulin.

Table 2. Baseline clinical and demographical characteristics per diagnostic group at final diagnosis ($_{Tfinal}$).
Abbreviations: SD=standard deviation, IQR=interquartile range, bvFTD: behavioural variant frontotemporal dementia; CSF = Cerebrospinal Fluid; FAB = Frontal Assesment Battery; FBI = Frontal Behavioral Inventory; FDG-PET = [^{18}F]-fluorodeoxyglucose-positron emission tomography; FT= frontotemporal; MADRS= Montgomery Asberg Depression Rating Scale; OND: other neurologic disease; PPD: primary psychiatric disorder; SRI = Stereotypy Rating Inventory.
Group differences: age at presentation (years): (ANOVA, F(2, 132)= 7.03, p<0.01), male gender %: (ɢ2 (1, N=133) =5.84, p=0.05), Education in years: (H(2)= 3.70, p=0.16), Disease Duration: (H(2)= 0.83, p= 0.66), Positive psychiatric history: (ɢ2 (1, N=133)= 8.94, p=0.01), FBI: (ANOVA, F(2, 130)=0.49, p=0.61), SRI: (H(2)=17.36 p<0.001), MADRS: (H(2)=11.45 p<0.01), MMSE: (H(2)= 1.34, p= 0.51), FAB: (H(2)= 5.91 p= 0.05), Ekman Faces (ANOVA, F(2, 103)=9.97, p<0.001), Neuropsychological (executive dysfunction): (ɢ2 (1, N=133)=0.19, p=0.91), MRI-brain (FT atrophy): (ɢ2 (1, N=133)=51.33, p<0.001), FDG-PET (FT hypometabolism): ɢ2 (1, N=87)=37.83, p<0.001).

Results with * differ significantly between the bvFTD and PPD group. Results with ± differ significantly between the PPD and OND group. Results with £ differ significant between the bvFTD and OND group.

Table 3. Clinical characteristics of patients switching diagnoses between T0-T2 and T2-T_{final}.

Abbreviations: SD=standard deviation, MRI=magnetic resonance imaging, FTD=frontotemporal dementia, FDG-PET=[^{18}F]-fluorodeoxyglucose-positron emission tomography.

Table 1. Diagnoses at baseline and final diagnosis (T_{final}).

	Baseline (T0)		**T_{final}**	
	n	**%**	**n**	**%**
Frontotemporal dementia total	**45**	**32.9**	**33**	**24.1**
Possible bvFTD	10	7.3	0	0
Probable bvFTD	45	32.8	29	21.2
FTD-ALS			*5*	
Definite bvFTD			4	2.9
Tauopathy			1	
C9orf72 expansion			2	
GRN-mutation			1	
Primary Psychiatric disorders total	**51**	**37.2**	**54**	**39.4**
Schizophrenia	2	1.5	1	0.7
Major depression	20	14.6	12	8.8
Minor depression	5	3.6	2	1.5
Obsessive Compulsive Disorder	2	1.5	0	0.0
Bipolar Disorder	6	4.4	6	4.4
Autism Spectrum Disorder	3	2.2	3	2.2
Personality disorder	2	1.5	5	3.6
Other psychiatric disorders problems	4	2.9	13	9.5
Relational problems	3	2.2	5	3.6
Subjective cognitive decline	4	2.9	5	3.6
Other Psychiatry	0		2	1.5
Other Neurologic disease total	**31**	**22.6**	**46**	**36.3**
Alzheimer's disease	7	5.1	9	6.6
Lewy Body Dementia	3	2.2	4	2.9
Vascular Dementia	2	1.5	7	5.1
Vascular MCI	4	2.9	3	2.2
Other Dementia	7	5.1	12	8.8

Other Neurology	8	5.8	11	8.0
Unknown	*0*		4	2.9
Total	*137*		*137*	

Abbreviations: bvFTD = behavioural variant Frontotemporal Dementia; FTD-ALS = Frontotemporal Dementia-Amyotrophic lateral sclerosis; *C9orf7*2 expansion = Chromosome 9 open reading frame 72 repeat expansion; *GRN* = progranulin.

Table 2. Baseline clinical and demographical characteristics per diagnostic group at final diagnosis ($_{Tfinal}$).

	bvFTD (n=33)	**PPD (n=54)**	**OND (n=46)**	**p-value**
Age at presentation (years), mean (SD)	63.3 (6.8)	59.6 (6.5)	64.4 (6.6)	**<0.01**[a]
Male gender, n (%)	19 (57.6)	44 (81.1)	33 (71.7)	0.05[b]
Education (years) median (IQR)	10.5 (4)	10 (4)	12 (5)	0.19[c]
Disease duration (years) median (IQR)	3.5 (7)	3 (2)	3 (3)	0.66 [c]
Positive psychiatric history, n (%)	8 (24.0) *	28 (51.9) *, ±	13 (28.3) ±	**0.01** [b]
FBI, mean (SD)	25.1 (9.3)	25.0 (9.1)	23.3 (10.0)	0.61 [a]
SRI, median (IQR)	9.5 (18) *, £	4 (8) *	1.5 (8) £	**<0.01** [c]
MADRS, median (IQR)	6.5 (11) *	12.5 (19) *, ±	6.5 (8) ±	**<0.01** [c]
MMSE, median (IQR)	27 (5)	27 (2)	26.5 (4)	0.51 [c]
FAB, median (IQR)	15 (4)	16 (5)	15.5 (3)	0.05 [c]
Ekman Faces Test, mean (SD)	30.8 (9.8) *, £	40.2 (7.5) *	37.5 (8.2) £	**<0.01** [a]
Executive dysfunction, n (%)	6 (18.2)	8 (14.8)	7 (15.2)	0.91 [b]
FTD like atrophy on MRI, n (%)	21 (63.6) *, £	2 (3.7) *	4 (8.7) £	**<0.001** [b]
FT hypometabolism on FDG-PET, n (%) [missing]	15 (93.8) *, £	13 (30.2) *	7 (22.6) £	**<0.01** [b]

Abbreviations: SD=standard deviation, IQR=interquartile range, bvFTD: behavioural variant frontotemporal dementia; CSF = Cerebrospinal Fluid; FAB = Frontal Assesment Battery; FBI = Frontal Behavioral Inventory; FDG-PET = [^{18}F]-fluorodeoxyglucose-positron emission tomography; FT= frontotemporal; MADRS= Montgomery Asberg Depression Rating Scale; OND: other neurologic disease; PPD: primary psychiatric disorder; SRI = Stereotypy Rating Inventory.
[a]One way ANOVA
[b] Pearson χ square analysis
[c]Kruskall Wallis test

Group differences: age at presentation (years): (ANOVA, F(2, 132)= 7.03, p<0.01), male gender %: (ɢ2 (1, N=133) =5.84, p=0.05), Education in years: (H(2)= 3.70, p=0.16), Disease Duration: (H(2)= 0.83, p= 0.66), Positive psychiatric history: (ɢ2 (1, N=133)= 8.94, p=0.01), FBI: (ANOVA, F(2, 130)=0.49, p=0.61), SRI: (H(2)=17.36 p<0.001), MADRS: (H(2)=11.45 p<0.01), MMSE: (H(2)= 1.34, p= 0.51), FAB: (H(2)= 5.91 p= 0.05), Ekman Faces (ANOVA, F(2, 103)=9.97, p<0.001), Neuropsychological (executive dysfunction): (ɢ2 (1, N=133)=0.19, p=0.91), MRI-brain (FT atrophy): (ɢ2 (1, N=133)=51.33, p<0.001), FDG-PET (FT hypometabolism): (ɢ2 (1, N=87)=37.83, p<0.001). Results with * differ significantly between the bvFTD and PPD group. Results with ± differ significantly between the PPD and OND group. Results with £ differ significant between the bvFTD and OND group.

Table 3. Clinical characteristics of patients switching diagnoses between T0-T2 and T2-T_{final}.

	T0 ï T2		**T2-T_{final}**	
	Switch	**No switch**	**Switch**	**No switch**
n (% total cohort)	29 (21.2)	92 (67.2)$^{n=16\ missing}$	8 (5.7%)	125 (91.2)$^{n=4\ missing}$
% male	79.3	69.6	75.0	72.0
Mean age at presentation (SD)	63.7 (6.4)	61.4 (6.8)	65.9 (4.6)	61.9 (7.0)
% MRI T2 made	75	70	75	63
MRI FTD like atrophy T0, +/-	3/26	22/70	1/7	26/99
FDG-PET FTD like pattern T0, +/-	11/14	19/40	1/7	34/48

Abbreviations: SD=standard deviation, MRI=magnetic resonance imaging, FTD=frontotemporal dementia, FDG-PET=[^{18}F]-fluorodeoxyglucose-positron emission tomography.