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The frontal lobe syndrome

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2016

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citation for published version (APA)

Krudop, W. A. (2016). *The frontal lobe syndrome: A neuropsychiatric challenge*.

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Part 1

THE FRONTAL LOBE SYNDROME



Chapter 1

GENERAL INTRODUCTION

DEMENTIA

The word *dementia* comes from the Latin *de-*, a prefix used to indicate departure or separation, and *mens* which stands for “mind” or “intellect”.

At present, dementia describes a syndrome in which there is deterioration of cognitive functioning, beyond what might be expected from normal aging. The cognitive impairment is progressive, will start to interfere with activities of daily living and will eventually lead to a loss of independence. This progressive dysfunction may occur within different cognitive domains. Memory functions, language skills, visuospatial and executive functioning (the higher-level cognitive skills you use to control and coordinate, for instance organization, planning and mental flexibility) may be affected, as well as social cognition, emotional control and the regulation of behavior.

It was estimated that worldwide 24.3 million people were suffering from dementia in 2001 and 35.6 million people in 2010 [1;2]. The prevalence of dementia is rising exponentially with the aging population and the affected number of people is expected to reach 115 million in 2050 [2;3].

Dementia can be brought about by several neurodegenerative disorders and a few non-degenerative causes, in the latter due most frequently to alcohol abuse and traumatic brain injury [4].

The most prevalent cause of neurodegenerative dementia is Alzheimer’s disease (AD) [5;6]. This disease was first described by the German neuropathologist and psychiatrist Aloïs Alzheimer [7]. In its most typical form, AD presents with memory problems, followed by impairments in visuospatial orientation, language, executive functioning or praxis (the inability to carry out a previously learned motor activity). A high age is the most important risk factor for AD and it is especially common in the older dementia population [1]. Nevertheless, up to 30% of the dementia patients are estimated to be below the age of 65 [4;8]. The etiologies of these *early onset* dementia cases (arbitrarily defined as an age of onset <65) have proven to be more difficult to diagnose, compared to those of *late onset* cases (≥ 65 years) [9;10]. This is not only because of the lower prevalence of all dementia sorts and the wider range of etiologies, but also because of the relatively frequent atypical presentation at a younger age [9-11]. Within the early onset dementia patients, Frontotemporal dementia (FTD) is the second most prevalent form with 2-22 per 100.000 aged 45-64 [5;12;12-15]. One study even found an equal prevalence for AD and FTD of 15 per 100.000



Aloïs Alzheimer

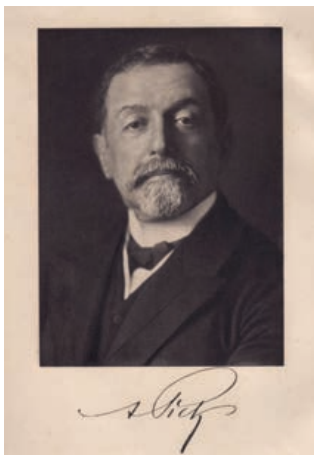
in early onset patients [16]. Nonetheless, also in older dementia patients FTD clinically seems to be prevalent more often than previously expected [12;17].

Frontotemporal dementia

The clinical syndrome presently defined as frontotemporal dementia (FTD) was first described by the Czech psychiatrist Arnold Pick in 1892 [18]. He portrayed a patient with behavioral abnormalities, aphasia and marked frontotemporal brain atrophy. Almost 20 years later, in 1911, Alois Alzheimer described the accompanying pathological inclusion bodies in more detail [19]. These inclusion bodies, known as Pick's bodies, resulted in the name of 'Pick's disease' as was used for many years for the clinical FTD syndrome. To date, Pick's disease is known to be one of the neuropathological subgroups of FTD [20].

The total neuropathological spectrum underlying FTD is called frontotemporal lobar degeneration (FTLD) and tissue deposition of abnormally aggregated proteins is the common pathological mechanism. The spectrum encompasses two main pathological subgroups and a number of rare variants. The main pathological findings are either accumulation of the hyperphosphorylated tau protein or accumulation of the transactive response DNA-binding protein 43 (TDP-43) [21;22]. A relatively small proportion of FTD results from accumulation of the fused-in-sarcoma (FUS) protein [22;23]. These three types of protein accumulation have been further classified into distinct subtypes, with only a small minority of FTD cases remaining in which the pathogenic inclusions are unknown [20;22;24].

FTD has a substantial genetic component, with an autosomal dominant inheritance pattern of pathogenic mutations in around 10-23% [13;21;22;24]. Some of the genes that cause FTLD are typically associated with a clinical picture of amyotrophic lateral sclerosis (ALS), the most common type of motor neuron disease (MND), and others with parkinsonian syndromes, progressive supranuclear palsy (PSP) or corticobasal syndrome (CBS) [21;22]. Several pathogenic mutations in genes encoding for different proteins have been identified: microtubule-associated protein tau (MAPT), progranulin (GRN), vasolin-containing protein (VCP) and charged multivesicular body protein 2B (CHMP2B) [22;24-26]. Furthermore, a nucleotide repeat expansion on chromosome 9 (C9orf72) causes FTD and/or ALS [24;27]. Family history is positive in up to 50% of patients [16;21;22].



Arnold Pick

Clinically, FTD encompasses three distinct syndromes: the behavioral variant of FTD (bvFTD) and two language variants: semantic dementia (SD) and

progressive non-fluent aphasia (PNFA) [28;29]. No consistent relationship between the histopathology and the clinical phenotype, which is largely determined by the distribution rather than the pathological type, has been found [22;26;30-32].

Behavioral variant frontotemporal dementia

BvFTD is characterized by profound behavioral and character change [29;33-38]. Three main behavioral syndromes have been recognized: the disinhibited syndrome, the apathetic syndrome and the stereotypical syndrome. Anatomically, these three main syndromes are each associated with specific frontal-subcortical circuits [34;39-41]. Nevertheless, mixed symptomatology between these syndromes is no exception and a wide range of sometimes aberrant behaviors may occur [29;33-35;37].

Patients often lose the ability to initiate action (accredited to the apathetic syndrome), or to inhibit inappropriate behavior and to evaluate their own behavior based on social cues from others (usually accredited to the disinhibited syndrome). In many cases 'environmentally dependent' behavior occurs, indicating that the behavior is heavily affected by external cues instead of being based on the patient's intrinsic motivation [42;43]. Furthermore, the frontal lobes are essential for regulating emotions and for the ability to judge the emotional and rational incentives of others; the so-called 'Theory of Mind' [24;44-47]. Therefore, bvFTD patients at times lose the ability to appropriately understand someone else's emotions, reasoning or thoughts when not explained, resulting in emotional bluntness and the disregard of social conventions, giving rise to both apathy and disinhibited behavior [24;45;48]. Furthermore, severe mental inflexibility and perseverative or stereotypical ritualistic behavior may occur (accredited to the stereotypical syndrome) [24].

The cognitive deteriorations described above inevitably lead to dementia in the course of the disease, but may be insidious at the early disease stages. The fact that one symptom can shift into another over time (for instance disinhibition changes into apathy) can conceal progression and therefore make clinical practice more complex. Since nearly all bvFTD patients suffer from a lack of insight or deny any form of illness, the information from a reliable informant is very important for the diagnosis, especially at an early stage. These first insidious symptoms usually present at an age of 45-60 (range 20-75 years), but 25% of bvFTD patients exhibits an age of onset after 65 years of age [14;16].

Frontotemporal dementia and the psychiatric differential diagnosis

The frontal lobes and the affected frontal-subcortical circuits play an essential role in regulating behavior: self-awareness, self-regulation, mental flexibility and the capacity for judgment and impulse regulation are under the executive control of the frontal lobes [41;49-53]. Many diseases, neurodegenerative as well as psychiatric, may result in either structural deterioration or dysfunction of these frontal-subcortical brain networks, leading to a so-called frontal lobe syndrome [4;5;17;41;46;52;54-61]. AD can present with a clinically

apparent frontal lobe syndrome and a specific ‘frontal variant’ of AD has been described, mimicking the bvFTD clinical phenotype [14;55;58;62-65]. Likewise, dementia with Lewy bodies (DLB) and vascular dementia (VaD) can both result in similar symptomatology [4;5;66].

Fortunately, recent research has made great progress in improving diagnostic biomarkers in Alzheimer’s disease, DLB and VaD [67-71]. Therefore, it has become easier to discriminate bvFTD from other neurodegenerative disorders. Nowadays, the main clinical dilemma is formed by the psychiatric differential diagnosis of bvFTD.

The psychiatric disorders possibly resulting in a similar frontal lobe syndrome are numerous [72]. Emotional blunting, apathy, economy of thought and speech are frequent symptoms of a psychiatric syndrome [73-78]. The negative symptoms in schizophrenia, depression, dysthymic disorder or autism spectrum disorders can involve the same frontal-subcortical circuits [57;61;75;79]. Similarly, in manic episodes, bipolar disorder, anxiety disorders, obsessive-compulsive disorder or tic syndromes, other behavioral disturbances as seen in bvFTD, like stereotypical language, motor or behavior disinhibition, occur [36;80-82]. Although psychiatric disorders typically establish during youth or young adulthood, they arise not infrequently at middle or even at older age [83-88].

Differentiating bvFTD from psychiatric causes of such a late onset frontal lobe syndrome is difficult in daily clinical practice, since the clinical overlap is great and no specific method to discern these two diagnostic groups exists. This results in frequent misdiagnosis with inaccurate or incorrect information on prognosis, progression, chances of recovery and over- as well as under-treatment. Up to 50% of bvFTD patients initially receive a psychiatric diagnosis [56]. Previous research also indicated that erroneously diagnosing psychiatric disease as *early onset dementia* is not uncommon but recent figures on this type of misdiagnosis are lacking [89;90].

The diagnostic difficulties are also illustrated by the fact that diagnostic delay in FTD patients is significantly longer compared to other dementia causes with an average symptoms onset to diagnosis time of 6.4 years [10].

The subtle and slowly progressive nature of bvFTD and the fact that patients often lack insight in their illness make it even harder to diagnose and determine the origin of the complaints at an early stage [10].

Diagnosing behavioral variant Frontotemporal dementia

For many years the Lund and Manchester criteria were used, but in view of the low sensitivity, new frontotemporal dementia consensus (FTDC) criteria were published in 2011 [91-95]. In these FTDC criteria, a degree of probability (*possible*, *probable* or *definite*) is assigned to the clinical diagnosis bvFTD, according to neuroimaging, genetic and pathological findings [92]. It is stated that a bvFTD diagnosis cannot be made in the presence of an explanatory psychiatric condition.

The sensitivity of the FTDC criteria has been assessed using an autopsy confirmed FTD cohort [92]. The specificity was 95% in a cohort using only AD and primary progressive aphasia patients as a control group, but still needs to be established in a broad differential diagnostic group including non-neurodegenerative frontal lobe causes [96;97]. So, although biomarkers take a prominent position in the present diagnostic criteria, it is still unclear how they can distinguish between bvFTD and non-bvFTD in a representative control group with frontal lobe syndrome symptoms [92].

The definition of ‘dementia’ as given in the DSM IV does not capture the clinical FTD syndrome [73]. The DSM-5 criteria for ‘cognitive disorders’ have been adapted in order to include neurodegenerative disorders not presenting with memory decline as a first symptom, making them more fitting for bvFTD [74]. Still, the clinician must decide if the cognitive deficits are not primarily attributable to another mental disorder, in which case no neurocognitive disorder may be diagnosed. Vice versa, before diagnosing a psychotic or mood disorder according to the DSM, one must exclude the possibility that the symptoms may be caused by an organic or neurodegenerative disorder. This illustrates clearly that in clinical practice, the diagnostic dilemma “bvFTD or psychiatry” is not solved by simply applying the different sets of clinical consensus criteria.

Neuropsychological testing may help to identify bvFTD cases, but has several limitations. The consensus criteria state that mainly executive function impairment with relative sparing of the visuospatial abilities and memory domain is supportive for underlying bvFTD and discriminates these patients from AD patients [92]. However, many FTD patients appear to have clear memory impairments or no specific dysexecutive profile compared to AD patients [22;92;98;99;99-101]. In fact, some studies show bvFTD patients to have impairment in nearly all cognitive domains and others show remarkably few abnormalities on neuropsychological tests [99;101;102]. Furthermore, a number of psychiatric disorders have shown to result in isolated executive function impairments as well [57;103]. Therefore, discrimination between the two conditions based on neuropsychological findings seems unreliable.

The sensitivity of magnetic resonance imaging (MRI) for bvFTD appears to be around 50-63.5 % [104;105]. The sensitivity is lowered by the fact that a substantial proportion of bvFTD patients show no apparent imaging abnormalities [106;107].

Disproportional symmetric or asymmetric frontal, temporal or frontotemporal atrophy may be present and may help to distinguish bvFTD from other conditions [92]. Medial temporal lobe atrophy may be present as well, indicating that this feature is not very specific for AD, compromising the imaging specificity for bvFTD [108]. Functional imaging is more sensitive to early changes in metabolism or function, when atrophy is not clearly apparent yet. A positron emission tomography (PET-)scan allows for visualization of a wide range of (patho)physiological processes, using different radioligands or PET-tracers [109]. One of the PET-tracers frequently used in examining brain diseases is [¹⁸F]-FDG-PET, specifically designed to visualize the glucose metabolism [109]. The glucose metabolism is related to

local brain function and can be seen in bvFTD typical patterns of hypometabolism [92;110]. However, especially in early FTD, functional imaging investigations may be normal as well [102]. Using [¹⁸F]FDG-PET with visual rating, imaging sensitivity rises to 81- 90% [105;110].

Unfortunately, both MRI and FDG-PET-scanning can result in frontotemporal abnormalities in psychiatric patients as well, further compromising the specificity of imaging for bvFTD [111-116].

Measuring CSF levels of Amyloid-beta, total Tau and phosphorylated Tau is mainly helpful to distinguish FTD from AD, but no specific pattern is found in FTD [117-122]. Also, recently, a decreased phospho-tau-181/total-tau ratio differentiated FTD with underlying TDP-43 pathology from FTD with underlying tau-pathology [123]. In psychiatric disorders like depression and schizophrenia CSF biomarker results have been found to vary between normal to slightly elevated total-tau and p-tau levels compared to healthy controls, but significantly lower than seen in AD [124-126]. All these findings need to be confirmed in future research, but clearly indicate the increasing knowledge of the potential use of CSF biomarkers in bvFTD and its differential diagnosis. Unfortunately, no specific CSF marker for bvFTD exists as yet.

So, not only the early age of onset, the absence of insight and the lack of a perfect diagnostic marker lead to diagnostic delay, but also the clinical overlap with psychiatric disorders hampers an early and accurate bvFTD diagnosis.

Importance of a correct bvFTD diagnosis

Every form of dementia is devastating, not only for the people who suffer from it, but also for their families, caregivers and friends. Compared to other forms of dementia, bvFTD has an even higher adverse effect on the carers and spouses of the patients in question: they perceive care-giving as a great burden and quite often unfortunately suffer from depression or anxiety disorders [10;127-129]. Since neurodegenerative disorders are progressive and will eventually lead to death, whereas most psychiatric disorders are treatable, an early and accurate diagnosis is highly essential. A correct diagnosis enables clinicians to start adequate treatment, support their caregivers and reliably estimate the prognosis. There is no disease modifying treatment available yet, but pharmaceutical trials are ongoing and when a potential treatment does become available it is important to be able to identify the etiology of the disease as accurately and as early as possible.

AIMS OF THIS THESIS

The aim of this thesis was to gain more insight into the spectrum of etiologies underlying a frontal lobe syndrome. To achieve this goal it was important to carefully define the clinical features of the frontal lobe syndrome in order to be able to standardize the inclusion procedure for further research questions. Further questions concerning the frontal lobe syndrome were investigated: what causes such a syndrome? Where are the pathological abnormalities located?

A frontal lobe syndrome is the typical presentation of bvFTD and bvFTD is known to be difficult to discern from other frontal lobe syndrome etiologies. Therefore, the next focus lay on identifying what this group of clinical disorders, symptomatically alike bvFTD, consists of in clinical practice. The frontal lobe syndrome arising at an age ≥ 45 was coined the 'late onset frontal lobe syndrome' (abbreviated 'LOF'). Accordingly, we intend to identify the actual relevant differential diagnosis of bvFTD in clinical practice.

Whereas many studies on screening instruments and biomarkers have focused on bvFTD versus other forms of neurodegeneration, this study focuses on the psychiatric differential diagnosis of bvFTD. We aimed to evaluate frequently used screening instruments and informant based questionnaires within this actual differential diagnosis. Also, the additional value of MRI, [^{18}F]FDG-PET and CSF-biomarkers in distinguishing the different neurodegenerative and psychiatric disorders from one another will be examined.

The present clinical approach is often mono-disciplinary, be it neurological or psychiatric. Our ambition was to design a study, approaching the clinical practice as much as possible, in which we could obtain information on the added diagnostic value of a multidisciplinary approach. Finally, characteristics of patients at risk for being misdiagnosed as early bvFTD were identified.

OUTLINE OF THIS THESIS

Chapter 2 of this thesis describes how the term *frontal lobe syndrome* was used historically through the ages, considering how the term is presently used in view of recent clinical and research developments. The most important milestones in the development of neurological and psychiatric disorders presenting with a frontal lobe syndrome are highlighted. The clinical overlap in disorders with diverse origins is discussed in accordance with recent findings in brain networks. In **chapter 3** the neuropathological findings of deceased patients who donated their brain to the Netherlands Brain Bank are presented. Subjects with a clinical frontal lobe syndrome during the course of their disease were selected and the distribution of the pathological abnormalities throughout the frontal-subcortical circuits is described. In **chapter 4** four cases with long-standing bipolar disease illustrate

another clinical dilemma. These patients fitted the FTDC criteria for possible bvFTD, but follow-up showed no indication of neurodegeneration. An end stage bipolar mood disorder might be explanatory for this phenotype. Furthermore, an interesting case, both fulfilling the FTDC criteria for probable behavioral variant frontotemporal dementia and the criteria for a late onset schizophrenia, is portrayed. The clinical dilemma and the value of ancillary biomarker results in the differential diagnosis are described, illustrating one of the possible clinical dilemmas arising in a LOF. In **chapter 5** the design and the most important outcome measures of our naturalistic prospective cohort study, the Late Onset Frontal lobe syndrome-study (LOF-study), are presented. We designated a LOF as newly developed behavioral disturbances after the age of 40 according to a reliable informant (inclusion of patients aged 45-75 years). In **chapter 6** the cross-sectional range of multidisciplinary diagnoses underlying the late onset frontal lobe syndrome in the LOF-study, is described. Furthermore the value of frequently used screening instruments and informant based behavioral questionnaires in differentiating between bvFTD and other frontal lobe syndrome causes is studied. In **chapter 7** the impact of neuroimaging markers, MRI and FDG-PET, and CSF biomarkers on the diagnostic certainty and on changes of diagnoses, is evaluated. This is examined within the LOF-cohort in the diagnostic process as carried out by the neurologist. In **chapter 8** the added value of the multidisciplinary approach in subjects with a bvFTD diagnosis made by a neurologist is examined. Blinded baseline diagnosis were compared to the final diagnosis after two years of follow-up and the subgroup with diagnostic changes is characterized. In **chapter 9** the main findings of this thesis are discussed and some recommendations for future research on this topic are outlined.

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