The frontal lobe syndrome

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Chapter 3

CLINICO-PATHOLOGICAL CORRELATIONS OF THE FRONTAL LOBE SYNDROME: RESULTS OF A LARGE BRAIN BANK STUDY

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ABSTRACT

Background/Aims: A clinical frontal lobe syndrome (FLS) is generally attributed to functional and/or structural disturbances within the frontal-subcortical circuits. We studied the distribution of pathological brain changes in patients with FLS due to various brain disorders. Additionally, the prevalence of FLS among these disorders was studied.

Methods: We systematically screened the clinical case notes of donors to the Netherlands Brain Bank (n=2814) for FLS based on clinical parameters. 262 FLS cases were identified and the distribution of post-mortem pathologic changes within the frontal-subcortical circuits was extracted from their neuropathological reports. We compared the prevalence of FLS among the various brain diseases.

Results: In 244 out of 262 (93%) patients pathological changes within the frontal-subcortical circuits were found. In 90 (34%) subjects frontal cortical pathology was found on examination. In 18 (7%) subjects pathological changes were restricted to the subcortical grey matter nuclei, whereas both cortical and subcortical regions were affected in 136 subjects (52%). In 18 (7%) subjects no pathology was found in the examined frontal areas. The prevalence of FLS was highest in frontotemporal lobar degeneration, followed by progressive supranuclear palsy and vascular dementia ($\chi^2(6, N=1561) = 222.64, p < .01$).

Conclusion: In this large brain bank study the distribution of pathological changes in subjects with FLS for the first time was shown to be frontal-subcortical. Only a minority of cases had FLS associated with pathology in the subcortical regions only or no frontal pathology at all.

INTRODUCTION

The term 'frontal lobe syndrome' (FLS) refers to the cognitive, behavioral and affective changes due to functional or structural deficits of either the prefrontal cortex or its connected subcortical structures [1-6].

Historically, three distinct functional neuro-anatomical circuits have been strongly associated with FLS: the dorsolateral prefrontal circuit, the orbitofrontal circuit and the medial frontal circuit [7-9]. These anatomically segregated as well as parallel loops run through the prefrontal cortex and striatum, globus pallidus, thalamus and project back to the cortex [7-9]. Several studies have shown a direct association between functional and structural connectivity [10]. The anatomically distinguishable frontal-subcortical circuits are also structurally as well as functionally connected [11-13]. Disruption of each circuit has been related to a specific behavioral symptom cluster (Table 1) [2;9;14;15]. Thus, not only frontal cortical lesions, but also lesions in the subcortical areas or the connecting white matter may lead to a FLS in clinical practice [4;7;9;12;15;16]. However, the distribution of neuropathological changes in FLS has never been studied neuropathologically.

Here, we hypothesized that subjects with FLS would show pathological abnormalities in either the frontal cortex, or the subcortical structures included in the three frontal-subcortical circuits, or both. We therefore aimed to investigate the anatomical distribution of pathology in subjects with FLS, derived from the total cohort of the Netherlands Brain Bank (NBB, Amsterdam, the Netherlands). We also compared the prevalence of FLS among the pathologically confirmed disorders.

METHODS

Case selection

2814 donated brains were collected by the Netherlands Brain Bank (NBB, Amsterdam, the Netherlands) between 1999 and 2011. A wide variety of medical conditions was registered and examined with the exception of donors with known Human Immunodeficiency Virus (HIV)-infection and a diagnosis of prion disease. Demographic variables, clinical features, clinical diagnosis and neuropathological findings were obtained.

Frontal lobe syndrome

Cases were classified as having a 'Frontal Lobe Syndrome' (FLS) when at least three out of 16 terms concerning cognitive, behavioral or affective changes were present (Table 1) [9]. These terms were generated based on the original anatomical-behavioral descriptions [7;9]. 262 subjects in this study fulfilled the FLS definition of having had at least three symptoms mentioned in Table 1.

We examined all clinical charts/notes of patients collected from the NBB (n=2814) in a blinded fashion for the parameters of FLS. When the definition for FLS was met, we investigated the standardized neuropathological reports.

Dorsolateral prefrontal circuit [1]	*Orbitofrontal circuit* [2]	*Medial frontal circuit* [3]
1. Impaired organization and planning	6. Inappropriate social behavior	13. Apathy
2. Poor concentration or distractibility	7. Compulsive or ritualistic behavior	14. Loss of initiative (or indifference)
3. Cognitive inflexibility	8. Imitation or utilization	15. Emotional indifference
4. Perseveration	9. Disinhibition	16. Loss of insight
5. Impaired problem solving	10. Euphoria	
	11. Irritability and/or aggression	
	12. Hyperorality	

Table 1: The three behavioral symptom clusters and their associated subcortical prefrontal circuits. [1] associated with circuit running through the middle frontal gyrus [2] associated with circuit running through the orbitofrontal cortex [3] associated with circuit running through the anterior cingulate. Frontal Lobe Syndrome (FLS): three or more symptoms presents of list of 16.

Pathological examination

The neuropathologists (A.J.M.R. or W.Ka.) examined the donor tissue using a standard (NBB) protocol. Tissue blocks were taken and pathological diagnosis was made in accordance with the NBB-protocol (www.brainbank.nl). Since this is a retrospective study, the neuropathologists were blinded for the study hypothesis and the behavioral ratings.

Brain autopsy was carried out within 4-8 hours from death according to the Legal and Ethical Code of Conduct of the NBB. Neuronal loss and gliosis were scored and routine staining was performed with haematoxylin–eosin, Bodian or Gallyas, methenamine-silver and Congo red. Tissue blocks were taken from the right hemisphere unless there was left-predominant atrophy in which case tissue from the left hemisphere was taken.

Immunohistochemistry was performed using primary antibodies against hyperphosphorylated tau (mouse anti human PHF-Tau Monoclonal Antibody (Thermo scientific MN1020) :1:500), ubiquitin (monoclonal mouse anti-Ubiquitin, clone Ubi-1, (MAB1510), Chemicon 1: 200000), β-amyloid protein (Monoclonal Mouse anti-Human Beta-Amyloid (DAKO) 1:500), α-synuclein (Mouse monoclonal antibody NCL-L-ASYN, clone KM51 (Novocastra) 1), p62 (Mouse Anti-p62 lck ligand (BD Transduction Laboratories, Becton Dickinson BV 1:1000), TDP-43 (Anti TDP-43, phospho SER409/410-2, Human (rabbit, Cosmo Bio Co LTD) 1:4000), and fused in sarcoma (Sigma-Aldrich anti-fused in sarcoma; 1:25–200 with initial overnight incubation at room temperature, following pressure cooking) and stained as described [17]. Primary antibodies were incubated overnight at -4°C. Endogenous peroxidase activity was inhibited by incubation

in phosphate buffered saline–hydrogen peroxide– sodium azide solution (100 ml 0.1M phosphate-buffered saline + 2 ml 30% H2O2 + 1 ml natriumazide) for 30 min. The Histostain-Plus broad-spectrum kit DAB (Zymed) was used, slides were counterstained with Mayer's haematoxylin and mounted in Entellan.

For this study the following regions of interest were included: the convexity of the frontal cortex ('medial frontal gyrus'), the anterior part of the cingulate gyrus (or 'anterior cingulate'), the substantia nigra, the caudate nucleus, the putamen and globus pallidus and the thalamus with the subthalamic nucleus.

The pathological diagnosis was made using the Braak and Alafuzoff criteria (2006) and the NIAA guidelines (Montine, 2012) for Alzheimer's disease (AD), the Brun and Gustafson criteria (1988) for vascular dementia (VaD), the multiple sclerosis (MS)-criteria (van der Valk and de Groot, 2000) and the Mackenzie consensus criteria for frontotemporal lobar degeneration (FTLD) (www.brainbank.nl) [18-22].

The presence or absence of pathological brain changes was rated for each area based on the post mortem reports (S.B. and Y.P. post mortem reports by W.Ka and A.J.M.R.). All pathologic changes were rated abnormal ('present'), with the exception of both minimal pathologic changes limited to the walls of small vessels, as well as minimal diffuse plaques and tangles within the normal range for the examined age group (as qualified by the pathologist A.J.M.R.). Acute large vessel infarction or hemorrhage causing death were not considered to be related to an FLS during life.

For the main diagnostic groups we calculated the prevalence of an FLS as the percentage of FLS among the total number of autopsied cases per diagnostic group.

STATISTICAL ANALYSES

Statistical analyses were performed using the IBM SPSS Statistics for Windows, version 20. Pearson's χ^2 tests were used to compare the number of patients with a FLS among the total number of autopsied cases per diagnostic group in the NBB ; a p-value below .05 was considered significant.

Ethical considerations

The Medical Ethical Committee of the VU University Medical Center of Amsterdam approved the study. From all these subjects a registration with a written informed consent was obtained for the post-mortem tissue donation and the permission to collect medical information from their physicians.

RESULTS

Demographics of the 262 cases (9% of the total of 2814) meeting the FLS criteria are shown in Table 2. 144 (55%) were male and 118 (45%) were female. The mean age of onset was 65 years (range 15-92 years, SD = 14) with a mean age of death of 73 years (range 27-98 years, SD = 12) resulting in mean disease duration of 7.7 years (range 1-50 years, SD = 6.3). For demographics for each diagnostic subgroup, see Table 2.

Pathological diagnosis	Count (% of total)	Sex, number of females (%)	Mean age of onset (range) years	Mean disease duration (range) years
AD	72 (28)	35 (49)	70 (36-92)	7 (1-16)
FTLD	74 (28)	33 (45)	60 (35-83)	7 (1-18)
PD/DLB	19 (7)	5 (26)	66 (40-81)	9 (1-35)
VaD	10 (4)	2 (20)	66 (45-81)	6 (1-9)
MS	7 (3)	2 (29)	32 (22-47)	18 (7-26)
AD+DLB	19 (7)	14 (74)	73 (53-86)	7 (2-14)
AD+VaD	5 (2)	2 (40)	81 (69-91)	6 (2-9)
PSP	14 (5)	5 (36)	71 (59-89)	7 (1-18)
no pathology	9 (4)	4 (44)	52 (26-80)	24 (2-50)
other*	33 (13)	16 (49)	63 (15-89)	6 (1-15)
total	262	118 (45)	65 (15-92)	8 (1-50)

Table 2: FLS subjects: diagnostic subgroup demographics
AD: Alzheimer's disease, FTLD: frontotemporal lobar degeneration, PD: Parkinson's disease, DLB: Lewy body dementia, VaD: vascular dementia, MS: multiple sclerosis, PSP: progressive supranulear palsy. *'other' contained: argyrophilic grain disease, multiple system atrophy, spinocerebellar ataxia, neuronal ceroid lipofuscinosis and malignant neoplasms.

The vast majority (n=244, 93%) of the total group of 262 subjects with a FLS showed brain pathology within at least one of the examined frontal cortical and subcortical areas. In 90 of these 244 subjects (34% of the total of 262 with an FLS) some form of pathology was merely found in the selected areas of the frontal cortex (medial frontal gyrus or anterior cingulate). Eighteen subjects (7% of the total) showed pathology in non-cortical grey matter areas within the frontal-subcortical circuits (thalamus, substantia nigra, caudate nucleus, putamen or globus pallidus). In 136 subjects (52%) some form of pathology was found in both the frontal cortex and the subcortical grey matter. The frontal cortical pathology was predominantly localized in the medial frontal gyrus or in both areas. Exclusive anterior cingulate pathology was rare. The frontal subcortical pathology was predominately localized in de caudate nucleus. A more detailed distribution is shown in Figures 1 and 2.

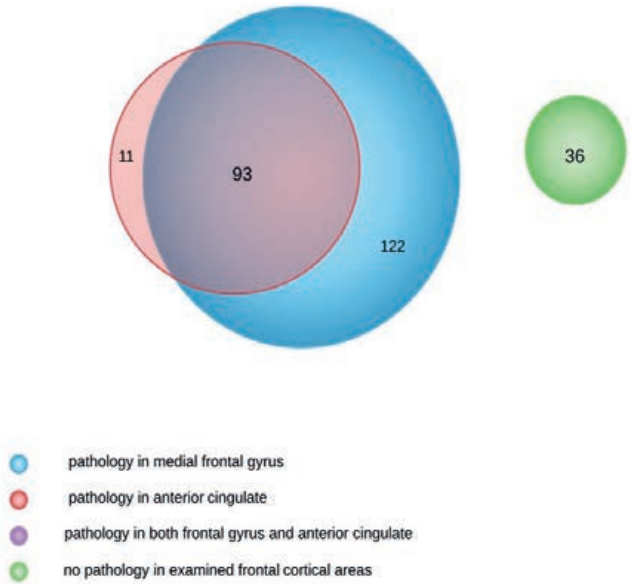

Figure 1: Distribution of pathology throughout the examined areas of the frontal cortex in the total group of 262 subjects with an FLS (subcortical pathology not taken into account)

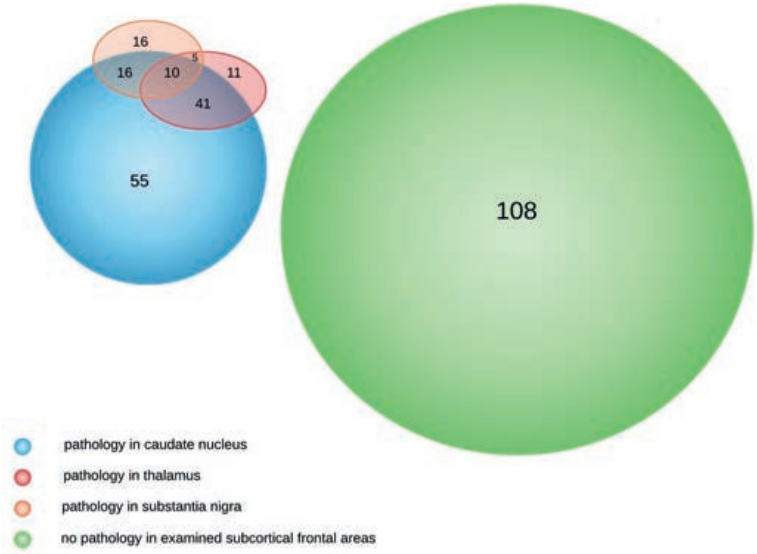

Figure 2: Distribution of pathology throughout the examined fronto-subcortical grey matter in the total group of 262 subjects with an FLS (frontal cortical pathology not taken into account)

Of the 90 subjects with mere frontal cortical pathology the majority (64%) was pathologically diagnosed with AD. The second most common pathological diagnosis within this group was FTLD (12%). Of the 18 subjects with mere frontal subcortical pathology FTLD (22%), VaD (22%), progressive supranuclear palsy (PSP, 17%) and Parkinson's disease/Lewy body dementia (PD/DLB, 11%) were diagnosed most frequently.

Of the 136 subjects with both frontal cortical and frontal subcortical pathology the majority was pathologically diagnosed as FTLD (43%), followed by AD (13%), DLB (12%) and PD/DLB (10%).

The remaining 18 subjects (262 minus 244, 7% of the total FLS-group) showed no pathology in either the cortical frontal areas examined nor the frontal basal ganglia and other frontal subcortical nuclei. Eight out of these 18 subjects without pathological abnormalities had a clinical psychiatric diagnosis (depression, bipolar disorder or schizophrenia) and showed, in accordance with this, no pathology at all in the examined frontal-(sub)cortical areas. The remaining group of 10 subjects without pathology within the examined areas (4% of the total group of FLS-subjects) included diagnoses of MS (n=4), alcohol dementia (n=1), hippocampal sclerosis (n=1), argyrophilic grain disease (n=1) and an unspecified tauopathy (n=1). Moreover, in 1 FTLD and 1 PSP subject no frontal pathology was found; however, in these two specific cases not enough post-mortem tissue was obtained for all immunohistochemistral stainings resulting in missing data.

Percentage of total NBB population with and without FLS and frontal pathology

Of the total NBB cohort 9% met the FLS definition (262 out of 2814). When subjects were grouped according to pathological diagnosis, the following FLS prevalence was found: 72 out of 785 AD subjects (9%; mixed pathology cases were excluded), 74 out of 145 FTLD subjects (51%; 31 FTLD-tau, 39 FTLD-TDP43 and 4 FTLD-FUS), 14 out of 52 PSP subjects (27%), 10 out of 74 VaD subjects (14%), 7 out of 202 MS subjects (3%), 19 out of 203 DLB/PD subjects (9%) and 8 out of 100 psychiatry cases (8%) (Figure 3). The prevalence of FLS differed significantly between the diagnostic groups ($\chi^2(6, N=1561) = 222.64$, $p < .01$). The percentage of FTLD as well as PSP cases was significantly higher compared to all other diagnostic subgroups shown in Figure 3. Differences also remained significant when excluding cases with an FLS without frontal pathology ($\chi^2(6, N=1547) = 245.13$, $p < .01$).

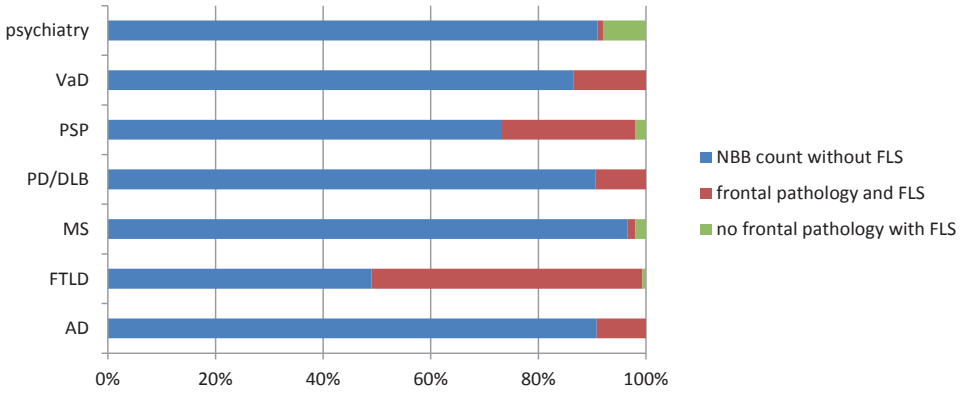

Figure 3: percentage of subjects with an frontal lobe syndrome (FLS) per diagnostic subgroup within the total Netherlands Brain Bank-cohort
NBB: Netherlands Brain Bank, VaD: vasculair dementia, PSP: progressive supranuclear palsy, PD/DLB: Parkinson's disease,/ dementia with Lewy bodies, MS: multiple sclerosis, FTLD: fronto-temporal lobar degeneration, AD: Alzheimer's disease

DISCUSSION

The distribution of pathological changes in subjects with FLS showed to be frontal-subcortical. The vast majority of subjects had either frontal cortical pathological abnormalities (in the medial frontal gyrus or cingulate gyrus) or frontal cortical as well as subcortical pathological abnormalities. Only a minority of cases had FLS associated with pathology limited to the subcortical regions or no frontal pathology at all [7;9].

As may be expected, we found that the frontal lobe syndrome was present relatively frequent in FTLD (51%) and in PSP (27%), versus 9% within the total NBB-group. This percentage seems remarkably low in the FTLD-group since in this diagnostic group the frontal lobe syndrome is obligatory for the diagnosis [23]. In addition, in most PSP cases frontal behavior disturbance is apparent as well, and apathy, utilization and imitation are considered diagnostic supportive criteria [24;25]. Taken together, these findings suggests underreporting of behavioral disturbances in the NBB-case notes. This said, part of the FTLD-cases may have had a more (unilaterally) temporally located variant with associated symptom clusters, possibly explaining absence of typical frontal behavior. This underreporting bias probably occurred in all diagnostic subgroups, so the proportional ratio of FLS between the different subgroups probably is a realistic representation. FLS is not uncommon in AD and other types of dementia [26]. The difference between our percentage of FLS in AD (9%) and VaD (14%), compared to the numbers others have found in clinical prevalence studies (50% and 49% respectively) also suggests underreporting [27]. In a clinical VaD cohort apathy was apparent in 65% and irritability in 42% [16]. Clinically

diagnosed PSP patients showed to have behavioral changes in 53% (compared to 27% in our pathological cohort) [24].

The majority of the group of subjects with mere frontal cortical pathology had an AD pathological diagnosis, while the subjects with subcortical frontal pathology showed far less AD pathology. Those subjects were pathologically diagnosed with a variety of disorders of which FTLD made out the largest group. Although subcortical involvement in FTLD is common, it has mainly been considered a focal cortical dementia [28;29]. Recent studies, however have clearly demonstrated the involvement of both the white matter and subcortical areas in this disorder. For example, in FTLD-FUS and FTLD caused by C9orf mutation there is marked involvement of the caudate and thalamic nuclei respectively [30].

The relatively small number of psychiatric subjects within both the FLS-group as well as the total NBB-cohort is striking. Many if not most psychiatric disorders show FLS features, so it is likely that the group of psychiatric patients with an FLS is especially underrepresented. It seems plausible that physicians point out the existence of brain donation more often to patients with specific diagnoses, especially the neurodegenerative diseases. This may lead to the above mentioned small subgroup of subjects with a psychiatric diagnosis as well as for instance lower numbers of vascular cognitive impairment or dementia as would be expected because of its prevalence in the population. Possibly, this 'referral' bias results in a lower number of subjects with mere subcortical pathology.

The lack of prospectively and systematically collected clinical data on patient behavior during life, forms a limitation to our FLS study design. Furthermore, the information on the cortical area of the orbitofrontal circuit is missing, since it is not included in the NBB pathologist protocol. This protocol limitation restricts the statement that 7% of the subjects has no frontal circuit pathology. An alternative explanation could be that the subjects without apparent frontal-subcortical pathology would show white matter tract pathology on examination, since these tracts are not included in the NBB protocol; therefore information on the white matter is unavailable.

It seems unlikely (especially in the subgroup with a psychiatric diagnosis) for these cases to have merely orbitofrontal pathology. However, of the 19 cases without proven frontal-subcortical pathology, 4 subjects had the clinical diagnosis MS; white matter demyelination within the frontal circuits seems plausible in this small subgroup.

The retrospective data collection, without the possibility of examining the time of onset of symptoms to the actual pathological examination, may result in another limitation, due to further spreading of pathology since the symptom onset. This mechanism could be responsible for some degree of overestimation of the number of pathologically affected areas.

To our knowledge, this is the first study attempting to relate clinical FLS to the distribution of its pathological anatomical correlates and combining a large amount of fundamental pathological data with recent insights in functionally connected networks [11-13]. Research

on the resting state functional networks (*salience network* and the *executive control network)* associated with FLS, confirm the link between the frontal cortex and the subcortical grey matter, even though the *executive control network* also includes some parietal regions that are not included in this study [7;9;13;31].

Another strength of this study is the symptom based inclusion. Despite the mentioned study limitations, the two methodologically strong points result in retrospective data with the highest level of diagnostic certainty possible, in a clinically relevant subgroup of patients with behavioral disturbances.

In clinical practice, due to the absence of typical clinical presentation or imaging abnormalities, neuropathological confirmation remains the gold standard for neurodegenerative diseases presenting with FLS [32;33]. Currently we are collecting prospective postmortem data in the Late Onset Frontal lobe (LOF)-study, overcoming the substantial shortcomings of retrospective data collection and underreporting of FLS [34].

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