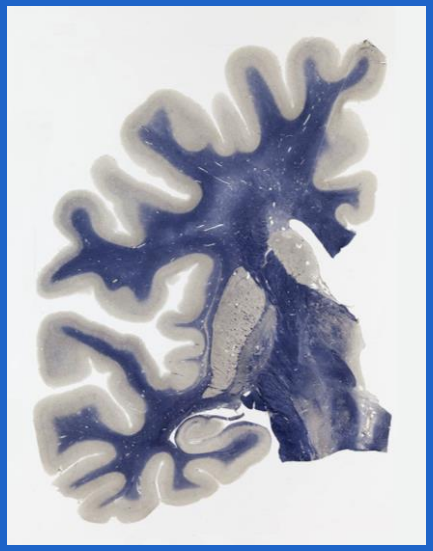
FACULTY OF MEDICINE AND HEALTH SCIENCES

Instituut BORN-BUNGE Universiteit Antwerpen

PROTEINOPATHIES OF FRONTOTEMPORAL LOBAR DEGENERATION

INVESTIGATING THE IMPACT OF VASCULAR CONTRIBUTIONS



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Summary

In the last decade, evidence has shown that dementia syndromes such as Alzheimer's disease (AD) and vascular dementia can be delayed or even prevented by changes in lifestyle and reduction of cardiovascular risk factors.

For other, less prevalent dementia syndromes, such as frontotemporal dementia (FTD) and its neuropathological correlate frontotemporal lobar degeneration (FTLD) this information is lacking.

FTLD is a collection of different protein aggregates, or proteinopathies, affecting the frontal and/or temporal lobes.

This thesis covers the neuropathological evaluation of a young onset FTLD cohort, with specific interest in vascular and other age-related alterations. In a review paper, the different **FTLD syndromes and their genetics** were described.

A first study included the creation of a **cohort of young onset FTLD** cases from the brain bank of the Institute Born-Bunge. The study resulted in 106 well characterized cases of which FTLD with TDP-43 pathology was most prevalent. A semi-quantitative rating of cerebrovascular pathology was also included in this study.

In a next study the **cerebrovascular pathology** was assessed in a 9 members of the **Belgian progranulin gene (*GRN*) founder family**. The neuropathological analysis in all cases showed FTLD-TDP type A, combined with mild AD, age-related tauopathy or Lewy body disease. Additionally, cerebrovascular disease (CVD) was also found and scored in every case.

Conclusions

FTLD is clinically, neuropathologically and genetically **heterogeneous** with plenty of overlap between the neurodegenerative mechanisms and the clinical expression thereof. This thesis demonstrates that proteinopathies are **not isolated events** in the aging brain. Other factors such as cerebrovascular pathology and with that the involvement of the blood-brain barrier should also be considered. We propose a multifactorial and multi-cellular disease concept in FTLD.

Next to TDP-43 proteinopathies, our FTLD cohort also consisted of cases with tauopathies. As **progressive supranuclear paralysis (PSP)** is the most common tauopathy, 7 PSP cases and 7 age matched control cases were neuropathologically examined to assess other comorbidities, including cerebrovascular pathology. A tendency of a higher CVD load was found in the PSP cases compared to the control cases.

Hippocampal sclerosis (HS) is a common finding in elderly patients, often associated with TDP-43, but also with CVD. In a next study, we confirmed the strong relation between HS and hippocampal TDP-43 pathology, and showed an additional association between HS and vascular changes in the deep white matter and basal ganglia. We hypothesize that both conditions act as a double hit on vulnerable hippocampal neurons and suggest that both conditions affect each other, driving neurodegeneration and the degradation of the blood-brain barrier, leading to sclerosis and neuronal loss.

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Curriculum Vitae

Anne Sieben graduated in 2009 as a neurologist. She combined clinical neurology in AZ Jan Palfijn Ghent with a staff position in the neurology department of the Ghent University Hospital, and with research in the neuropathology lab of the Institute Born-Bunge, University of Antwerp. In the Ghent University Hospital she subspecialized in cognitive neurology, participated in many clinical trials and is part of the Cognitive Centre of University (Hospital) of Ghent. She is also a certified LEIF doctor and was member of the Ethical Committee of the AZ Jan Palfijn. In 2021 she started a training in Pathological Anatomy in the Antwerp University Hospital and combines this with the research in the IBB. She is (co)author of 50 A1 publications.

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