



**Karolinska
Institutet**

Institutionen för Neurobiologi, Vårdvetenskap och Samhälle
Sektionen för Alzheimer Neurobiologi Center

**A Multi-tracer PET Approach to Study
Early-onset Familial and Sporadic Alzheimer's Disease**

AKADEMISK AVHANDLING

av

Michael Schöll

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Karolinska Institutet, Karolinska Universitetssjukhuset Huddinge

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Huvudhandledare:

Professor Agneta Nordberg
Karolinska Institutet
Institutionen för Neurobiologi,
Vårdvetenskap och Samhälle

Bihandledare:

Professor Ove Almkvist
Institutionen för Neurobiologi,
Vårdvetenskap och Samhälle

Professor Bengt Långström
Uppsala Universitet
Institutionen för biokemi och organisk
kemi

Fakultetsopponent:

Professor William Jagust
University of California Berkeley
Helen Wills Neuroscience Institute

Betygsnämnd:

Professor Lars Nyberg
Umeå Universitet
Umeå Center for Functional Brain Imaging
Institutionen för integrativ medicinsk
biologi

Professor Irina Alafuzoff
Uppsala Universitet
Institutionen för immunologi, genetik och
patologi

Docent Steen Hasselbalch
Københavns Universitet
Neurobiology Research Unit, Rigshospitalet

Abstract

Cumulated scientific evidence suggests that the pathology causing Alzheimer's disease (AD) occurs many years or even decades before memory impairment and other clinical symptoms arise. Tangible and detailed knowledge about different pathological processes, their interactions, and time course is therefore of the essence both for the development of potentially successful treatments and a reliable early diagnosis of this relentless disorder. The past decade has thus seen an explosion in research on biomarkers that could provide *in vivo* evidence for these pathological processes, involving β -amyloid ($A\beta$) production and aggregation into plaques, neurofibrillary tangle formation, neuroinflammation, and eventually neurodegeneration.

The rare form of dominantly-inherited early-onset familial AD (eoFAD), with almost complete mutation penetrance and defined age of disease onset, has been proposed as a model to study the very early disease mechanisms that are also supposed to underlie the common sporadic form (sAD). However, more than 200 mutations in three different genes (*PSEN1 and 2, APP*) have been identified as causing eoFAD, some of which have been shown to differ substantially from others.

This work employed multi-tracer positron emission tomography (PET), using the tracers 2- ^{18}F -fluoro-2-deoxy-D-glucose (FDG), *N*-methyl- ^{11}C 2-(4'-methylaminophenyl)-6-hydroxy-benzothiazole (PIB), and ^{11}C -L-deuterium-deprenyl (DED) to explore the characteristics, time course and interrelationship of cerebral glucose metabolism, fibrillar $A\beta$ burden, and astrocyte activation (astrocytosis) at different presymptomatic and symptomatic disease stages of eoFAD and sAD, in relationship to cognition, other AD biomarkers, and/or *post-mortem* pathology.

Thalamic hypometabolism in *PSEN1* eoFAD mutation carriers was demonstrated in this thesis nearly 20 years before they were expected to develop clinical symptoms. The pattern of hypometabolism studied in several mutation carriers spread subsequently to regions that are also typically affected in sAD, correlating well with cognitive decline at symptomatic disease stages. Regional hypometabolism was furthermore found to correlate with typical AD pathology, namely neuritic $A\beta$ plaques at *post-mortem* examination, suggesting that FDG PET is an excellent marker of disease progression from early presymptomatic stages to terminal disease.

One particular eoFAD mutation, the Arctic *APP* mutation, has been reported to modify amyloid processing in a way that obviates the formation of fibrillar $A\beta$, the form of $A\beta$ most prone to aggregate into neuritic plaques. In contrast to carriers of other eoFAD mutations and sAD patients, we found that carriers of the Arctic *APP* mutation showed no cortical PIB PET retention as a measure of fibrillar $A\beta$ load, while $A\beta$ and tau in cerebral spinal fluid and glucose metabolism, and in advanced disease also medial temporal lobe atrophy as measured by magnetic resonance imaging and cognition were clearly pathological and typical of AD. The findings imply that clinical AD can be caused by forms of $A\beta$, supposedly oligomeric or protofibrillar, which cannot be detected by PIB PET.

Very little is still known from *in vivo* studies about when and where in the brain neuroinflammation occurs in AD. Here, it could be shown that DED binding as a measure of astrocytosis was elevated in prodromal AD patients, whereas binding levels in AD were comparable to those in controls. PIB PET retention was increased and glucose metabolism decreased in both groups and there was no regional relationship between the three tracers, indicating that astrocytosis is an early phenomenon in AD that follows a different spatial and temporal pattern than $A\beta$ plaque deposition and impaired synaptic activity as measured by glucose metabolism.

Multi-tracer PET is in this work proven to provide novel insights in eoFAD and sAD pathogenesis with processes such as astrocytosis and the potential role of different $A\beta$ species. This knowledge is of significance for the understanding of disease mechanisms as well as the comparability of the purely genetic and the sporadic form of AD.