Project: Role of chronic viral infection on the neuropathological presentation and the pathophysiology of Alzheimers disease

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Background and preliminary data:
There is increasing evidence supporting the involvement of the neuroimmune system in neurodegenerative diseases such as Alzheimer's disease (AD). Several epidemiological and experimental studies suggest that systemic viral infections may elevate the risk of developing dementia (1). In particular, chronic viral infections can induce persistent, low-grade neuroinflammation, potentially influencing the aggregation, deposition, and clearance of AD-associated proteins in the brain. Such processes may contribute to synaptic damage, neuronal dysfunction, and the progressive neurodegenerative changes characteristic of AD.

The recent COVID-19 pandemic provided a unique opportunity to study the impact of chronic viral infection on neurodegeneration. A substantial proportion of individuals with COVID-19 exhibited systemic inflammation and an activation of the neuroimmune system (2). Elevated plasma biomarkers associated with AD pathology have been reported in COVID-19 patients (3). However, the neuropathological changes linking chronic viral infection in this instance - SARS-CoV-2 infection- to the pathogenesis and presentation of AD remain poorly understood.

To investigate the influence of subacute to chronic COVID-19 on AD pathology, we have established age- and sex-matched autopsy cohorts of patients (n=12 for each group) with (i) AD alone, (ii) COVID-19 alone, and (iii) combined AD and COVID-19. The assembly of these cohorts has been greatly facilitated by intensified autopsy efforts at UKE during the pandemic and through collaboration within the national autopsy network, providing access to a broad range of autopsy samples from university hospitals across Germany (4).

To ensure unbiased and high-throughput assessment of the type and amount of β-amyloid and phosphorylated tau pathology, but also of neuroimmune activation in the central nervous system (CNS), we have established a machine learning–based image analysis pipeline. This approach enables quantitative evaluation and classification of disease-associated protein aggregates and immune cell activation on digitized whole-slide images from four carefully selected brain regions per patient.

Hypothesis:
We hypothesize that the neuroimmunological activation seen in COVID-19 patients leads to specifically perturbed inflammatory and protein deposition pathways, and differential neuropathological presentation of AD. By neuropathological deep phenotyping and assessing region and cell-specific transcriptomic differences, we will identify biologically relevant pathways linking chronic viral infection to AD pathogenesis (5).

Aims and Work Programme:

Aim 1: Neuropathological Deep Phenotyping to unravel influence of chronic viral infection on the neuropathological presentation of AD
We will perform detailed neuropathological analyses of brain tissue from patients with AD alone, COVID-19 alone, and combined AD and COVID-19. Specific pathological and neuroinflammatory markers will be assessed across key brain regions (frontal cortex, temporal cortex, and hippocampus).
Protein aggregates including β-amyloid, α-synuclein, phosphorylated tau (pTau), and TDP-43 but also neuroimmune activation markers (HLA-DR, Iba1, P2RY12, TMEM119, CD32, CD163, CD3, CD4, CD8, and CD20) will be quantified and categorized using

immunohistochemistry followed by morphometric analysis via our machine learning–based platform.

Aim 2: Pathway analysis to unravel how chronic viral infection affects the pathophysiology of AD

To gain mechanistic insight into how chronic viral infection alters the molecular landscape of AD pathology, we will perform spatial transcriptomics using the Xenium platform. To maximize efficiency and reduce resource consumption, we will employ tissue microarray (TMA) technology, allowing small tissue cores from representative brain regions to be assembled on a single paraffin block.

Integrating morphological and molecular datasets will enable multi-omics analysis through algorithms available at the Institute of Neuropathology (6). This approach will allow us to identify region-specific transcriptional changes and immune signaling pathways associated with chronic viral infection and AD co-pathology.

Project-related publications:

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5. Sepulveda-Falla D, Chavez-Gutierrez L, Portelius E, Vélez JI, Dujardin S, Barrera-Ocampo A, Dinkel F, Hagel C, Puig B, Mastronardi C, Lopera F, Hyman BT, Blennow K, Arcos-Burgos M, de Strooper B, Glatzel M. A multifactorial model of pathology for age of onset heterogeneity in familial Alzheimer's disease. Acta Neuropathol. 2021 Feb;141(2):217-233.

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