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The NO-Age and NO-AD Seminar Series 024

'Amyloid and tau pathology in Alzheimer's disease: Neuropathology in symptomatic and presymptomatic cases'

by

Prof. Dietmar Thal

Katholieke Universiteit Leuven, Belgium

at

14:00-15:00 (CET), Monday, 19th April 2021

Register in advance for this webinar:

https://uio.zoom.us/webinar/register/WN_bYm0QgKYTrKePgI7I64GBg

Organizers:

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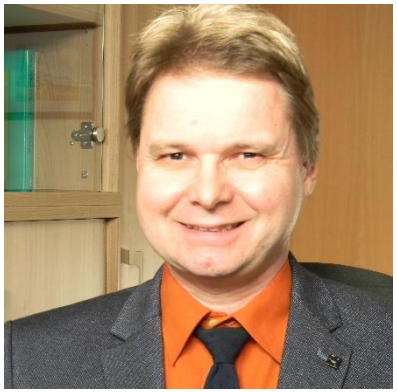

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Speaker: Dietmar Thal

Title: Amyloid and tau pathology in AD: Neuropathology in symptomatic and presymptomatic cases

Abstract:
Alzheimer's disease (AD) is the most frequent cause of dementia in elderly individuals. Its neuropathological hallmark lesions are senile plaques consisting of aggregates of the amyloid β protein (Aβ) and neurofibrillary tangles (NFTs) representing fibrillar aggregates of abnormal phosphorylated τ-protein (p-τ). Aβ plaques and NFTs do not only occur in symptomatic AD patients. They can also be seen in brains of non-demented individuals. Based upon topographical staging systems describing the distribution of Aβ plaques and NFTs in the human brain it became evident that non-symptomatic cases with Aβ and NFT pathology show early stages of the pattern observed in symptomatic AD cases. In those brain regions that become involved into Aβ or p-τ pathology in symptomatic AD cases Aβ plaques and NFTs show a similar sequence of aggregate maturation as in other regions already developing pathology in asymptomatic cases. I.e. plaques first contain only Aβ lacking pyroglutamate formation or phosphorylation before AβN3pE can be found. AβpSer8 is restricted to only a few cases, usually symptomatic AD cases. p-τ phosphorylated at specific sites of the τ-protein accumulates first as IC-(initial cytoplasmic pT231-τ) and IN-tau (initial neuropil pS396/pS404-τ) before pretangles are formed exhibiting multiple phosphoepitopes of τ incl. pS202/pT205 and later develop into argyrophilic NFTs. These steps in the development of NFTs are observed in the entorhinal region before the respective cases are become demented whereas a similar maturation of τ pathology in the primary cortex and the cerebellum is observed in symptomatic AD. Thus, there is a propagation Aβ and p-τ pathology in the development of AD starting a similar maturation process in all regions once a given region becomes affected. To clarify which Aβ and p-τ species are involved in this process we tested distinct types of human brain tissue-derived brain lysates to induce Aβ and p-τ pathology in APP and TAU transgenic mouse models. We will show the seeding characteristics of different Aβ and p-τ preparations received from brain lysates. The results indicate that multiple types of Aβ aggregates can induce Aβ seeding while sarkosyl-insoluble p-τ showed superior seeding effects compared to more soluble forms of brain-lysate derived p-τ confirming previous results from other groups.

Biography:
Prof. Thal is neuropathologist and professor for Neuropathology at KU-Leuven (Belgium) with his main research focus on AD. His major interest is the expansion and maturation of protein aggregates in AD. He was able to discover phases describing the expansion of amyloid plaque pathology in the human brain. These phases are currently included in the diagnostic criteria for the neuropathological assessment of Alzheimer's disease (known as Thal-Phases).
Prof. Thal could show that the current amyloid PET-methods are usually restricted to the detection of moderate - advanced phases of amyloid plaques pathology distribution and in so doing represent a valuable tool for diagnosing the symptomatic disease and advanced stages of preclinical AD but not for picking up very early stages of the disease. When including the caudate nucleus SUVRs he was able to estimate the amyloid (Thal) phases with phase 3 being the earliest.
In addition, his group able to show that not only the anatomical expansion of amyloid plaque aggregates plays a role in the pathogenesis of AD but also the maturation of the aggregates, meaning that the composition of amyloid plaque/soluble and dispersible amyloid aggregates changes over time with specific proteins becoming detectable only in the symptomatic cases. Recently, his group found that the interaction of Aβ with cellular prion proteins appeared to accelerate the spreading of τ-pathology in AD.
The major goals of his further research are: 1) To improve the preclinical detection of AD and other neurodegenerative disease to allow treatment before significant neuron loss has started; and 2) to identify critical steps in the cascade of protein aggregate maturation and its link the neuron loss in AD that can be tackled for therapeutic purposes.