Dietmar Thal and the Alzheimer ABC

The initial consensus guidelines for the postmortem diagnosis of Alzheimer’s disease were published in 1997. In the same year, Dietmar Thal started his four-year research project at the Institute of Anatomy at the University of Frankfurt under the supervision of Heiko Braak, who was then one of the leading figures in Alzheimer’s research, notably for his achievements in grading the presence and distribution of tau tangles in the brain in 1991. In 2012, Dietmar Thal took up where Braak had left off and became a member of the group of experts tasked with updating the 1997 guidelines.

Dietmar Thal, 45, has been professor of neuropathology at the University of Ulm since 2007 and is one of two Europeans on an otherwise all-American panel that revised the 1997 consensus guidelines for the neuropathologic evaluation of Alzheimer’s in 2012 (doi: 10.1016/j.jalz.2011.10007). Thal was well qualified to participate in the expert panel: in addition to the six distinct stages of Alzheimer’s progression named after his former supervisor, Thal has come up with a model, commonly referred to as Thal phases, which classifies amyloid beta protein (Aβ or Abeta) into five stages. In addition to abnormal tau proteins, Aβ plaques are regarded as the major hallmark of Alzheimer’s pathogenesis. The 2012 guidelines enlarge the assessment area of Alzheimer’s disease through the inclusion of neuritic plaques, which Thal refers to as ‘intersection of tau and Aβ’, i.e. “those Aβ plaques that have tau-positive dystrophic neurites”.

Between 1997 and 2012, major advancements were made in knowledge relating to Alzheimer’s disease, which is why a consensus panel convened in 2012 to update the 1997 guidelines. The 2012 panel recommends the ABC score for assessing neuropathological changes in Alzheimer’s (A for amyloid beta, B for Braak neurofibrillary tangle staging protocol, C for the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) neuritic plaque scoring system). Dietmar Thal knows from his own experience that it is difficult to come up with guidelines for diseases with a pathogenesis as complex as that of Alzheimer’s and for which no cure is available. According to the current state of knowledge, Alzheimer’s disease progression follows three stages: a recently recognised preclinical phase, which is free of disease symptoms, a phase characterised by mild cognitive impairment, which eventually develops into the third phase, i.e. dementia.

Initial anatomy lectures left a lasting impression

Dietmar Thal did his medical studies in his native town of Frankfurt and also attended lectures given by Heiko Braak. He was impressed by what Braak was teaching his students and became
interested in morphology and pathology. In the early nineties, Braak published what is now commonly referred to as Braak staging, a model that classifies Alzheimer’s into six pathological
stages based on the topographical distribution pattern of neurofibrillary changes and which led to him becoming the “god of neuropathological Alzheimer’s research”.

It is also thanks to Braak that Thal started specifically focussing on A\(\beta\), which is one of the two major hallmarks of Alzheimer’s pathogenesis. “I can blame my former supervisor for my interest in A\(\beta\),” said Thal with a smile, commenting on his four-year research period under Braak’s supervision. “Somebody in Braak’s institute had to take over Braak’s work on A\(\beta\).” Thal has been working on A\(\beta\) ever since; he habilitated on the topic, carried out animal experiments and contributed to expanding the biochemical understanding of the complex biomolecule. He also focused his research on the soluble amyloid aggregations that have a neurotoxic effect and on finding out which mechanisms cause the A\(\beta\) peptide to aggregate and become toxic.

When Thal joined Braak’s laboratory in 1997 and started focussing on A\(\beta\), he benefited enormously from Braak’s technical preparatory work and the open and friendly environment of the internationally respected institute. Although many researchers were working on A\(\beta\), Thal’s approach was new: he decided to focus initially on the anatomic distribution of the plaques, find out where they appear and how they spread in the brain. Thal points out that in 1997 nobody was aware of preclinical Alzheimer’s cases, referring to the observation that brain damage that leads to dementia starts developing many years before patients develop typical Alzheimer’s cognitive problems.

Clinical symptoms eventually convinced sceptics

Different brain areas develop amyloid beta deposits in a distinct hierarchical sequence: in the first phase, A\(\beta\) deposits are found exclusively in the neocortex (black); the second phase is characterised by the additional involvement of allocortical brain regions (red); in phase 3, the interbrain and the striatum exhibit A\(\beta\) deposits as well; several brainstem nuclei become involved in phase 4, and phase 5 is characterised by the occurrence of A\(\beta\) deposits in the cerebellum and other brain areas.

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Thal’s presentation of early Aβ stages initially faced great opposition; Heiko Braak had previously also suggested that Alzheimer’s developed over a long time and that typical Alzheimer’s deposits could be found in the brains of people who are completely asymptomatic. This scepticism was eventually dispelled with clinical findings that showed that Aβ deposition in non-demented elderly people was actually the first step in the pathogenesis of Alzheimer’s.

The central argument of Thal’s phase model is that Aβ spreads systematically in the brain, thereby replacing the general assumption that the peptide was omnipresent and proliferated. Based on the investigation of serial thin brain sections of patients of different age groups, Thal found that the deposition of Aβ starts in the neocortex and during the course of the disease spreads to other brain regions, i.e. allocortical and subcortical areas such as basal ganglia, brain stem and cerebellum.

He found that amyloid and tau aggregates appear simultaneously in different areas in the brain, but subsequently take different routes. “At first we regarded the plaques as lesions and found it difficult to understand how they were able to spread in the brain. The situation changed when we chose to regard soluble Aβ as lesions, because soluble Aβ can already be detected in the brain at a time when Aβ plaques are not yet present.”

Thal carried out research using transgenic animal models and discovered specific concentrations of soluble and less soluble Aβ aggregates in mouse brains. Thal believes that a specific level of less soluble Aβ aggregates needs to be reached (and therefore change homeostasis) before visible alterations can be seen. He compared transgenic mice which expressed amyloid precursor protein (APP) with mutated (leads to familial Alzheimer’s disease) and non-mutated Aβ. Mice that expressed normal APP had hardly any plaques, nor did they reveal cognitive deficits and morphological neuronal alterations.

Amyloid beta can bind to many proteins

Thal uses animal models to find out when the disease shifts from the preclinical stage to the clinical stage and attempts to transfer the situation to human Alzheimer’s pathology. If the assumption that the soluble version rather than the insoluble version of Aβ is neurotoxic proves to be correct, the researchers will have a lot of work ahead of them. They will have to develop a method that enables them to identify soluble Aβ without modifying it. The peptide is a hard nut to crack, even for amyloid experts like Thal who likes to compare the peptide with a magnet. The Aβ peptide is between 40 and 42 amino acids long and can be modified at different residues, especially at the terminal ends. Such modifications might lead to pyroglutamate Abeta peptides (pyroGluAβ), which easily form structurally distinct and toxic oligomers. The phosphorylation of Aβ and the binding of nitrate residues has also been found to trigger the formation of toxic aggregates. Although the researchers succeeded in classifying protein aggregates consisting of different APP cleavage products, they have not yet been able to elucidate their function. Thal calls this challenge a “new dimension of Aβ aggregation” and believes that Aβ aggregation is governed by the same mechanisms as prion, tau, synuclein and TDP-43 aggregation.

Thal believes that Aβ peptides clump together without requiring specific binding partners. In fact, many different proteins bind amyloid beta peptide and mediate neurotoxicity in Alzheimer’s disease. “Older scientific papers refer to many different proteins that are present in Aβ plaques,” said Thal, who has plans to investigate post-translationally modified Aβ species in the Aβ plaques in the human AD brain, characterise them biochemically and find out the Aβ species of different aggregate pools. If these findings can be systematised, Thal plans to transfer them into mouse models.
Thal believes that disease-associated Aβ structures will eventually be discovered and that immunotherapies will be targeted more precisely against disease-associated forms of Aβ. However, he also believes that extensive basic research will be necessary before it is possible to use PET (positron emission tomography) for immunising amyloid-beta positive individuals – if indeed it is ethically justifiable. Another immunotherapy against Alzheimer’s might involve a simple Aβ antibody, an approach that has already been tried out, albeit too late in the disease process. “On the other hand, many other factors might play a role in the pathogenesis of Alzheimer’s,” said Thal alluding to the aspect of comorbidity which was extensively covered in the 2012 consensus guidelines.

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