Advances in Deep Neuropathological Phenotyping of Alzheimer's disease: Past, Present, and Future

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Intro:

Alzheimer's disease (AD) is a neurodegenerative disorder characterized pathologically by the presence of neurofibrillary tangles (NFTs) and amyloid beta aggregates in the brain. It was first described in 1906 by Alois Alzheimer, and it is currently the most common cause of dementia worldwide. This paper delves into the past, present, and future outlook for AD, focusing on historical microscopy & staining advancements, disease heterogeneity, and improved neuropathological phenotyping through the use of machine learning.

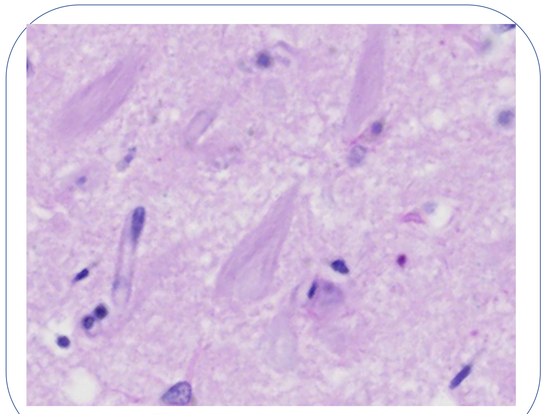


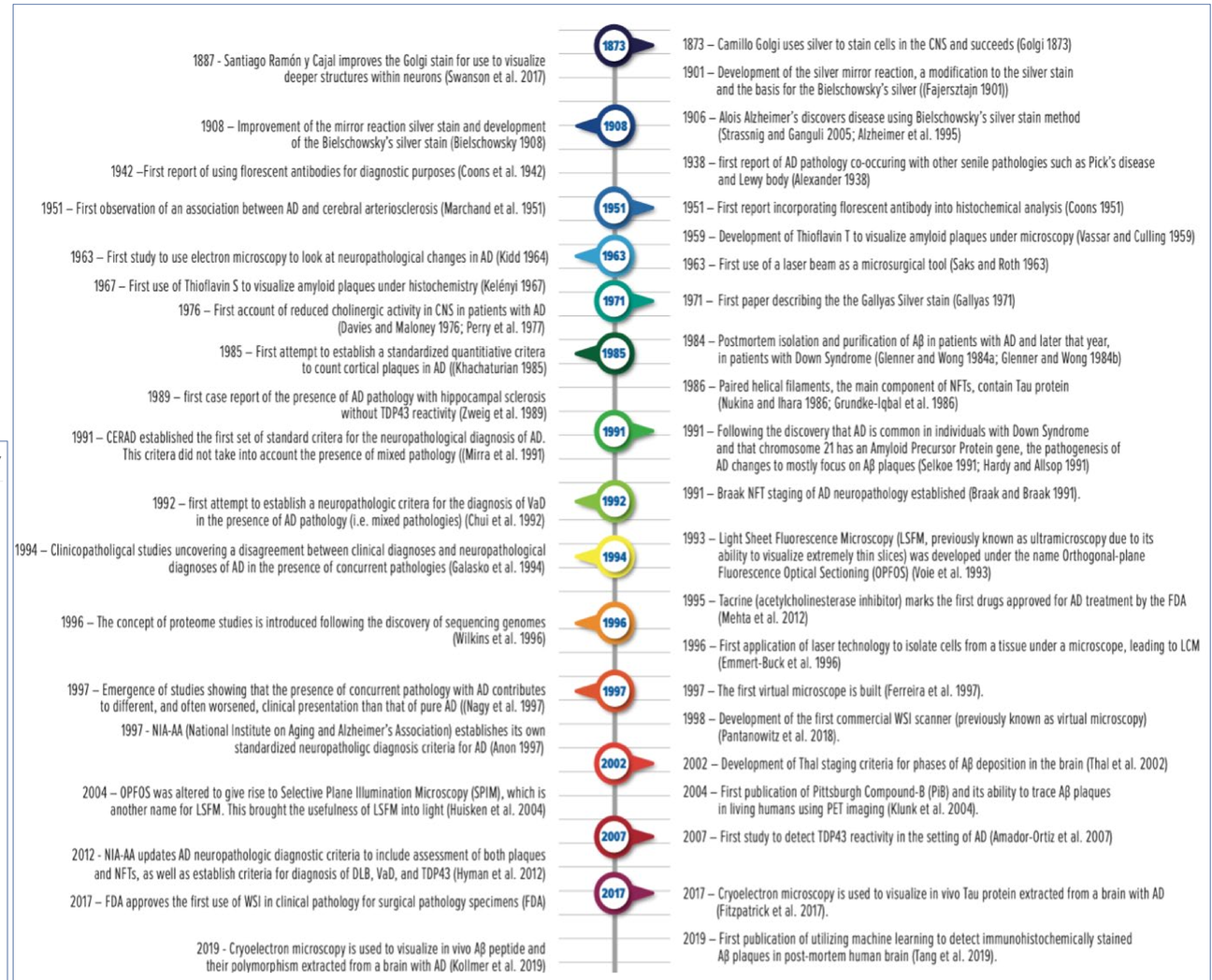
Image of an NFT on H&E stain

Diagnostics and heterogeneity:

- The neuroanatomical distribution of the amyloid plaques and NFTs are predictable, and there are multiple staging schemes (i.e. Thal phases for and Braak staging, respectively) that give a semi-quantitative score based on this presence of these pathologies in specific brain region.
- AD is a very heterogenous disease; it has different subtypes and often presents with other neurodegenerative pathologies (most commonly Lewy Body dementia, TDP-43 dementia, and vascular dementia).
- The presence of co-pathology can create a synergistic effect clinically. And physician are often driven to assign a single clinical diagnosis when there are multiple different pathologies histologically. This often leads to a disagreement between the clinical diagnosis and the neuropathological one, as well as a decrease in sensitivity and specify for the clinical diagnosis (see table).

Clinical Diagnosis	Neuropathological Diagnosis	Sensitivity	Specificity
AD	AD alone	0.56	0.82
	AD alone or with other pathology	0.46	0.88
VaD	VaD alone	0.56	0.83
	VaD alone or with other pathology	0.43	0.86
FTD	FTLD alone	0.75	0.94
	FTLD alone or with other pathology	0.69	0.95
AD +	AD + VaD alone	0.14	0.92
VaD	AD + VaD alone or with other pathology	0.17	0.92
DLB	LBD ± AD alone	0.42	0.98
	LBD ± AD alone or with other pathology	0.33	0.98
CJD	CJD alone	0.63	1.00
	CJD alone or with other pathology	0.50	1.00

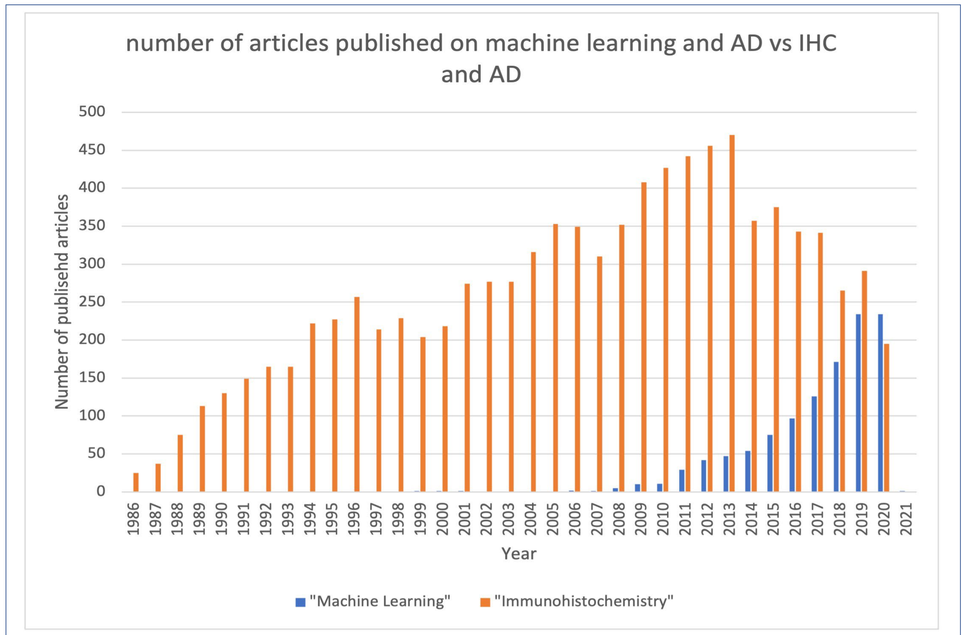
Specificity and sensitivity for AD with other neurodegenerative diseases (Brunnström et. al)



Timeline figure for historical events in AD

Machine learning and precision medicine:

- Given the current semi-quantitative approach to analyzing the neuropathology of AD, and the potential decrease in inter-rater reliability between different neuropathologists, there has been continuous efforts to improve the neuropathological phenotyping of AD. One way to do this is through machine learning (see graph).
- Establishing a better phenotyping of AD can pave the way to establishing a Precision Medicine model for disease management, which can lead to improved outcomes.



Comparing number of publications for AD and immunohistochemistry vs AD and machine learning

Conclusions:

- We have come to learn that AD is a very heterogenous disease, and establishing a better neuropathological phenotyping, perhaps through machine learning, may aid in improving our understanding of the disease and lead to better management of it.
- While machine learning seems like the ultimate answer, there are some caveats to consider, such as the complexity of developing an algorithm that can learn from a specific set of cohorts and then be applied to bigger, more diverse cohorts. Recent studies are immerging to show that this is possible.

Support:

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