How neuropathologic observations have determined the diagnosis and treatment of neurologic diseases: Emphasis on Dementia

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HV Vinters financial disclosures/conflicts:

- HVV is involved in studies aimed at optimizing ligands for amyloid imaging in the brain, which may be of commercial value
- Through a rev living trust, HVV owns shares in, & receives dividends from, companies that are developing diagnostic biomarkers (including neuroimaging methods) for AD, and novel treatments. These include General Electric, Teva Pharma, Pfizer Pharma, and Glaxo SmithKline Beecham

Neurodegenerative diseases....USA Prevalence

Alzheimer’s disease (SDAT) 5.3 million
Parkinson’s disease 400,000-1,000,000
Amyotrophic lateral sclerosis (ALS/MND) 16-17,000
Frontotemporal lobar degeneration(s) ? 50-100,000

United States Age Groups: Projected % Growth 2000-2020

Father of modern psychiatry; believed in the ‘physical/morphologic’ basis of psychiatric diseases

Coined the term ‘dementia praecox (schizophrenia); worked with Nissl & Alzheimer

History of the study of neuropsychiatric and neurodegenerative diseases— from a morphologic perspective

- A history that is relatively brief (begins late 1800s)
- AD first described in 1906, public’n in 1907
- By 1909, only 5 additional cases published—between ages 45 & 67; first subject (Auguste D.) almost certainly a familial case
- Staining methodology (esp. silver stains) crucial in evolution of our understanding of AD

First description of AD

Clinicians by day, histopathologists by night

Various academic posts in Germany (Frankfurt, Heidelberg, Munich)

Clinical record...of the first AD patient, 1906
First observation of senile plaques—in the brains of deceased epilepsy patients...
One of the fathers of modern Neurohistology / Neuroanatomy

Developed silver impregnation techniques used today in many NP laboratories

Senile plaques (silver stain)
CONTRIBUTIONS of NEUROPATHOLOGY to DEMENTIA RESEARCH - 1

Early 1900s: Classic descriptions of AD neuropathology—routine & silver stains. SPs, NFTs, CAA all characterized.

1960s-1970s: Correlative clinicopathologic studies established AD as the commonest cause of dementia (Blessed-Tomlinson-Roth 1968, 1970).

Empirical cyto/immunohistochemical (IHC) & E/M approaches to looking at AD lesions.

1980s-1990s: Isolation of AD lesions and the proteins that constitute them—Glenner & Wong, 1984—characterized Aβ/Beta amyloid from isolated meningeal CAA; Masters et al characterized SP core protein.

‘Rational’ IHC using primary antibodies to AD proteins (Aβ, p-Tau, others)—Terry et al, importance of synaptic loss in disease progression.

Characterizing neuropathologic component of AD Tg animal models.
Established clin-path correlation.....imperfect though it remains!!
CONTRIBUTIONS of NEUROPATHOLOGY to DEMENTIA RESEARCH - 1

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Characterizing neuropathologic component of AD Tg animal models
Mouse hippocampi in ABeta overproducing mice......
Physical Basis of Cognitive Alterations in Alzheimer’s Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment


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Abstract

We present here both linear regressions and multivariate analyses correlating three global neuropsychological tests with a number of structural and neurochemical measurements performed on a prospective series of 15 patients with Alzheimer’s disease and 9 neuropathologically normal subjects. The statistical data show only weak correlations between psychometric indices and plaques and tangles, but the density of neocortical synapses measured by a new immunocytochemical/densitometric technique reveals very powerful correlations with all three psychological assays. Multivariate analysis by stepwise regression produced a model including midfrontal and inferior parietal synapse density, plus inferior parietal plaque counts with a correlation coefficient of 0.96 for Mattis’s Dementia Rating Scale. Plaque density contributed only 26% of that strength.
CONTRIBUTIONS of NEUROPATHOLOGY to DEMENTIA RESEARCH -2

2000s: Recognition of the ‘universe’ of non-AD dementias---including DLBD, FTD spectrum

New diseases ‘caused by/related to’ new genes and proteins: Tau, TDP-43, FUS, alpha-synuclein progranulin, C9ORF (FTD-ALS)

Importance of AD-parenchymal-vascular co-morbidity in dementia pathogenesis---role of hippocampal ischemic injury?

Validating neuroimaging data (PiB, FDDNP, etc.)

2000s+++: Disease-modifying approaches---will they lead to structural ‘footprints’ in the brain?

Diagnostic criteria for staging AD Neuropathology

- Khachaturian (1985)
- CERAD (1990s)—stress neuritic plaques
- Braak & Braak (1990s)—stress NFT distribution
- NIA-Reagan Institute (1998)—”probabilistic"
CLINICAL SYNDROME

• Memory impairment
• Cognitive decline
• Focal motor/sensory deficits
• Personality change

(Autopsy)

NEUROPATHOLOGIC FEATURES

• Cortical atrophy, synapse and dendrite loss
• SPs, NFTs, CAA
• Microglial, astrocyte activation
• Microvessel-mediated ischemic changes

References


