Original Article

Biomarker Controversies and Diagnostic Difficulties in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) can be difficult to diagnose particularly in the earlier stages of illness when the symptoms are mild. In April 2011, National Institute on Aging(NIA)-Alzheimer's Association published a new criteria for diagnosing AD revised to that of the NINCDS-ADRDA Alzheimer's Criteria proposed in 1984 by the National Institute of Neurological & Communicative Disorders & Stroke and the Alzheimer's Disease & Related Disorders Association (now known as The Alzheimer's Association).As per 1984 criteria the diagnosis of AD is mostly based on Neuropsychological assesment for possible & probable AD, while it needs Autopsy for Definite AD.The new 2011 criteria includes certain phases of dementia & 5 biomarkers which helps in improving an earlier clinical diagnosis of AD i.e preclinical AD(presence of AD pathology in the absence of symptoms & signs of dementia). The Aβ deposition & elevated tau can be seen even in other neuropsychiatric disorders other than AD which created the diagnostic dilemma.

Keywords: Neurofibrillary tangles, Neuritic plaques, Alzheimer's Disease.

INTRODUCTION

Alzheimer's disease (AD),first characterized by Alois Alzheimer is a gradually progressive dementia affecting cognition, behaviour, and functional status. Neurofibrillary tangles(Tau protein) and Neuritic plaques(Amyloid beta deposition) are the pathological hallmarks of Alzheimer's disease.Neurofibrillary tangles are also present in several conditions such asLytico-bodig disease[1], Meningioangio-matosis[2], subacute sclerosing panence-phalitis[3] (SSPE), Dementia pugilistica[4], Pick's disease[5], Progressive supra nuclear palsy[6], Ganglioglioma[7], Argryophilic grain disease[8], Huntington's disease[9], Hallervorden-spatz disease[10]. Neuritic plaques are seen in Cerebral amyloid angiopathy[11], Temporal lobe epilepsy[12] which shows that there is a need for the development of biomarkers for an early and definitive diagnosis.Early assessment & diagnosis helps in providing an effective

pharmacological therapy and betterment of health care of the patient.

The 1984 NINCDS-ADRDA (National Institute of Neurological & Communicative Disorders & Stroke and the Alzheimer's Disease & Related Disorders Association) Criteria for diagnosis of probable Alzheimer's disease[13]

1. History of progressive cognitive decline of insidious onset by in-depth interview of patient & caregivers.
2. Deficits in atleast 2 or more areas of functioning.
3. No disturbance of consciousness by confirmation with use of dementia scaling rate. (Mini mental state examination or Blessed dementia scale).
4. Age between 45 & 90 years.(usually >65 years).
5. No other explainable causes of symptoms. (Normal laboratory tests,normal EEG,Normal physical exam including neurologic exam,Neuro-imaging-CT or MRI scanning showing no focal lesions or other possible causes of dementia.

The 2011 NIA(National Institute of Aging)-Alzheimer's association diagnostic criteria[14]

The pathological mechanisms are classified into 3 stages:

1. **Pre-clinical Alzheimer's disease-** Newly defined stage which reflects the current evidence that biomarker changes in the brain may occur before symptoms affecting the cognitive, non cognitive & functional abilities.
2. **Mild cognitive impairment (MCI) due to Alzheimer's disease-** More research is needed to distinguish those with MCI who will go on to develop Alzheimer's dementia from those who will not. Biomarkers, as they become validated, may help increase diagnostic accuracy in research settings.
3. **Dementia due to Alzheimer's Disease-** Emphasized the need for ruling out other causes of cognitive decline & documenting progressive decline over time. The diagnosis of Alzheimer's dementia may not always have memory impairment as its most central characteristic; a decline in other aspects of cognition (such as word-finding, vision/spatial issues, and impaired reasoning, judgment, and problem solving) may be the presenting or most prominent symptoms at first.

For research, diagnostic certainty may be improved by incorporation of certain biomarker measures.

The 2013 DSM-V (Diagnostic and Statistical Manual of Mental disorders, 5th edition.) criteria for Alzheimer's and Dementia[15]

- The term Dementia is replaced with neuro-cognitive disorder and mild neuro cognitive disorder which focussed on decline rather than deficit in function.
- Biological markers for Alzheimer's disease appear well before the onset of symptoms such as memory problems and functional impairment.
- The combination of symptoms and biomarkers (Aβ, Tau) support significantly that mild neurocognitive disorder will progress to major neurocognitive disorder.

Sensitive & specific biomarkers are yet to be identified for most of the neurocognitive disorders.

DISSCUSSION

Clinical Presentation of Ad

Globally Alzheimer's disease is under reported due to several reasons. The reasons include

1. The brain changes quite slowly over a period of time before actual symptoms are apparent. The family members often complain of the cognitive(memory loss,

disorientation, impaired executive function, Aphasia, Apraxia and Agnosia, non-cognitive (Behavioral and psychotic symptoms in dementia-hallucinations, delusions, physical & verbal aggression, motor hyperactivity, wandering, repetitive manner is ms, combativeness) and functional symptoms (In abilty in self care such as eating, dressing, bathing and toileting).

2. The family members may feel that these symptoms are normal with ageing.

3. The patient is not aware of his own abnormal behaviour & impaired executive functions.

DIFFRENTIAL DIAGNOSIS

The two major biomarkers which aids in the diagnosis of Alzheimer's disease include Aβ protein (Amyloid beta) and T protein (Tau).

Biomarkers of Aβ accumulation-

- Abnormal retention of beta-amyloid identifying tracer compounds on positron emission tomography (PET) imaging[16].
- Low levels of beta-amyloid 1-42 in cerebrospinal fluid (CSF)[17].

Biomarkers of Tau accumulation-

- Elevated levels of the protein tau (both total and phosphorylated tau) in CSF[18].
- Decreased fluorodeoxyglucose 18F (FDG) uptake on PET imaging in a specific pattern involving the brain's temporo-parietal cortex[19].

Atrophy on structural magnetic resonance imaging (MRI), again in a specific topographic pattern involving the brain's medial, basal &lateral temporal lobes and medial - lateral parietal cortices[16].

Recent Advances

Dr. Jie Xiang and colleagues from Taiyuan, University of Technology, China construsted brain networks using resting-state functional MRI data that were extracted from Four populations (normal controls ,patients with early mild cognitive impairment, patients with late mild cognitive impairment, and patients with AD) using the AD Neuroimaging initiative data set[21].

Results showed that as cognitive deficits increased across four groups, the shortest path in resting state functional network gradually increased, while clustering coefficients gradually decreased. This evidence indicates that dementia is associated with decline of brain networks efficiency .In addition, the changes in functional networks revealed the progressive detoriation of network function across brain regions from healthy adults to those with mild cognitive impairment and AD[21].

St. Jude Children's research hospital scientists have identified that plaques decreased substantially in mice treated with gene therapy to increase activity of the enzyme. neuraminidase 1(NEU1) in a region involved in learning and memory. NEU1 belongs to a family of enzymes in cells whose job is to dismantle and recycle unneeded proteins and other components. The result raises hopes the enzyme could lead to new methods of diagnosing and treating AD[22].

The findings include evidence of how the protein fragments that make up Alzheimer's plaque are deposited outside neurons and how loss of NEU1 possibily contributes to disease progression and spread. Within weeks of using gene therapy to bolster NEU1 activity,d' Azzo's laboratory group reported that plaques declined dramatically in the hippocampus of treated mice[22].

Columbia University medical center(CUMC) researchers have clarified three fundamental issues about Alzheimer's: where it starts, why it starts there, and how it spreads by using high resolution functional MRI(fMRI) imaging in patients with AD and in the mouse models of the disease[23].

1. It begins specifically in the lateral entorhinal cortex or LEC, which plays a major role in the consolidation of long-term memory[23].
2. In long term, AD spreads from the LEC directly to other areas of the cerebral cortex, in particular, the parietal cortex[23].
3. LEC dysfunction occurs when changes in tau and amyloid precursor protein (APP) co-exist[23].

CONCLUSION

Alzheimers disease affects multiple areas of cognition and is characterized by a gradual onset with a slow, progressive decline. Neuritic plaques and neurofibirally tangles are though hallmarks of disease but are also seen in other disease states and is difficult to differentiate from AD, So it would be better if researchers develop specific biomarkers for AD for early assessment and management to prevent the mortality and morbidity. Research related to NEU1 suggest that not only is NEU1 deficiency a risk factor for developing AD but this enzyme could be used to slow or even reverse the disease process .This concludes the current available biomarkers are controversial in the early diagnosis of AD. So the 2011criteria suggested biomarkers and the 2013 DSM-V criteria for Alzheimer's and Dementia wouldn't be used to diagnose or exclude AD but it would help in improving diagnostic accuracy in individuals with cognitive decline. However there is still a need for improving biomarkers & diagnosing tools which must be quick, easy & inexpensive with high specificity & safety.

REFERENCES

1. Sadayuki Matsumoto, Asao Hirano, Satoshi Goto, *et al*. **Spinal cord neurofibrillary tangles of Guamanian amyotrophic lateral sclerosis and parkinsonism-dementia complex.** *Neurology June 1990 vol. 40 no. 6 975,doi: 10.1212/WNL.40.6.975*
2. Batra A, Prayson RA, *et al*. **Meningioangiomatosis associated with focal cortical dysplasia and neurofibrillary tangles.** *Clin Neuropathol. 2013 Jan-Feb;32(1):37-41. doi: 10.5414/NP300501.*
3. Deniz Yuksel, Deniz Yilmaz, Neval Y. Uyar, Nesrin Senbil, Yavuz Gurer, Banu Anlar, et.al. **Tau proteins in the cerebrospinal fluid of patients with subacute sclerosing panencephalitis.** *Brain and DevelopmentVolume 32, Issue 6 , Pages 467-471, June 2010.*
4. Tommy Saing, Malcolm Dick, Peter T. Nelson, Ronald C. Kim, David H. Cribbs, Elizabeth Head,*et al*. Frontal Cortex Neuropathology in Dementia Pugilistica. *Journal of Neurotrauma. April 10, 2012, 29(6): 1054-1070. doi:10.1089/neu.2011.1957.*
5. Mathis CA, Klunk WE, *et al* **Imaging tau deposits in vivo: Progress in viewing more of the proteopathy picture.** *Neuron. 18 Sep 2013(79):1035-7.*
6. Armstrong, RA, Cairns, *et al*. Spatial patterns of the tau pathology in progressive supranuclear palsy. *NJ; (2013) Neurological Sciences, 34 (3), pp.337-344.*
7. Raffo S, Rubio A, Rodenhouse TG, Patel U, Bonfigilo T, Powers JM, *et al*. September 2001: 51-year-old man with seizures since childhood. *Brain Pathol. 2002 Jan;12(1):137-9.*
8. Grinberg LT, Wang X, Wang C, Sohn PD, Theofilas P, Sidhu M, Arevalo JB, Heinsen H, Huang EJ, Rosen H, Miller BL, Gan L, Seeley WW, *et al*. Argyrophilic grain disease differs from other tauopathies by lacking tau acetylation. *Acta Neuropathol. 2013 Apr;125(4):581-93.doi: 0.1007/s00401-013-1080-2. Epub 2013 Jan 31.*

9. De Calignon, *et al*. ***In Vivo* Spreading of Tau Pathology.** *Neuron, Volume 73, Issue 4, 621-623, 23 February 2012.*
10. Yuichi Riku**,** Takeshi Ikeuchi**,** Hiroyo Yoshino**,** Maya Mimuro**,** Kazuo Mano**,** Yoji Goto**,** Nobutaka Hattori**,** Gen SobueandMari Yoshida**,***et al*. Extensive aggregation of α-synuclein and tau in juvenile-onset neuroaxonal dystrophy: an autopsied individual with a novel mutation in the *PLA2G6* gene-splicing site. *Acta Neuropathologica Communications 2013, **1**:12 doi:10.1186/2051-5960-1-12.*
11. D'Angelo, Olivia M; Dooyema, Jeromy; Courtney, Cynthia; Walker, Lary C; Heuer, Eric, *et al*. Cerebral Amyloid Angiopathy in an Aged Sooty Mangabey (*Cercocebus atys*). *Comparative Medicine, Volume 63, Number 6, December 2013, pp. 515-520(6).*
12. Ina Caesar, Sam Gandy ,*et al*. **Evidence that an APOEε 4 'double whammy' increases risk for Alzheimer's disease.** *Medicine 2012,10:36 http://www.biomedcentral.com/1741-7015/10/36 (13 April 2012).*
13. Guy McKhann, David Drachman, Marshall Folstein, *et al*. **Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease.** *Neurology 1984;34;939 DOI 10.1212/WNL.34.7.939.*
14. Andrew E Budson,Paul R Solomon, *et al*. **New diagnostic criteria for Alzheimer's disease and mild cognitive impairment for the practical neurologist.** *Pract Neurol 2012;12:88-96 doi:10.1136/practneurol-2011-000145.*
15. Dan Blazer, *et al*. **Neurocognitive Disorders in DSM-5.** *Am J Psychiatry 2013;170:585-587. doi:10.1176/appi.ajp.2013.13020179.*
16. Ahmadul Kadir, Amelia Marutle, Daniel Gonzalez, Michael Scholl,Ove Almkvist Malahat Mousavi ,Tamanna Mustafiz ,Taher Darreh-Shori,Inger Nennesmoand and Agneta Nordberg. Positron emission tomography imaging and clinical progression in relation to molecular pathology in the first Pittsburgh Compound B positron emission tomography patient with Alzheimer's disease. *Brain (2010)doi: 10.1093/brain/awq349.*
17. Contino, M., Cantore, M., Leopoldo, M. and Colabufo, N, *et al*. **Biomarkers for the early diagnosis of Alzheimer's disease: The challenge of XXI century.** *Advances in Alzheimer's Disease, 2, 13-30. doi: 10.4236/aad.2013.21003.*
18. M Sjogren, P Davidsson, M Tullberg, L Minthon, A Wallin, C Wikkelso, A-K Granerus, H Vanderstichele, E Vanmechelen, K Blennow, *et al*. **Both total and phosphorylated tau are increased in Alzheimer's disease.** *J Neurol Neurosurg Psychiatry 2001;70:624–630.*
19. Manja Lehmann, Pia M. Ghosh, Cindee Madison[2], Robert Laforce Jr[1] ChiaraCorbetta-Rastelli, Michael W. Weiner, Michael D. Greicius, William W. Seeley, Maria L. Gorno-Tempini, Howard J. Rosen, Bruce L. Miller, William J. Jagust and Gil D. Rabinovici, *et al*. **Diverging patterns of amyloid deposition and hypo-metabolism in clinical variants of probable Alzheimer's disease.** *Brain (2013) 136 (3): 844-858.doi: 10.1093/brain/aws327.*
20. Marc, *et al*. **The plaques and tangles of Alzheimer's.** *Dementia SOS.*

Colorado's Dementia News & Research center.
http://dementiasos.files.wordpress.com/2011/12/dem-plaque-tangle.jpg

21. Xiang J, Guo H, Cao R, Liang H, Chen JJ , *et al*. **An abnormal resting-state functional brain network indicates progression towards Alzheimer's disease.** *Neural Regen Res. 2013;8(30):2789-2799.*
22. Annunziata I, Patterson A, Helton D, Hu H, Moshiach S, Gomero E, Nixon R, d'Azzo A, *et al*. **Lysosomal NEU1 deficiency affects amyloid precursor protein levels and amyloid-β secretion via deregulated lysosomal exocytosis.** *Nat Commun. 2013 Nov 14;4:2734. doi: 10.1038/ncomms3734.*
23. Usman A Khan, Li Liu, Frank A Provenzano, Diego E Berman, Caterina Profaci, Richard Sloan, Richard Mayeux, Karen E Duff ,Scott A Small, *et al*. **Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease.** *Nature Neuroscience 17,304–311(2014)doi:10.1038/nn.3606***.** Berkeley,CA.

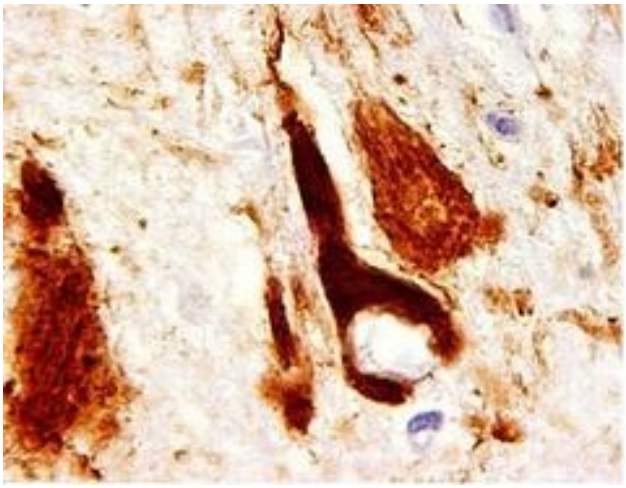

Figure 1. Neurofibrillary tangles[20]

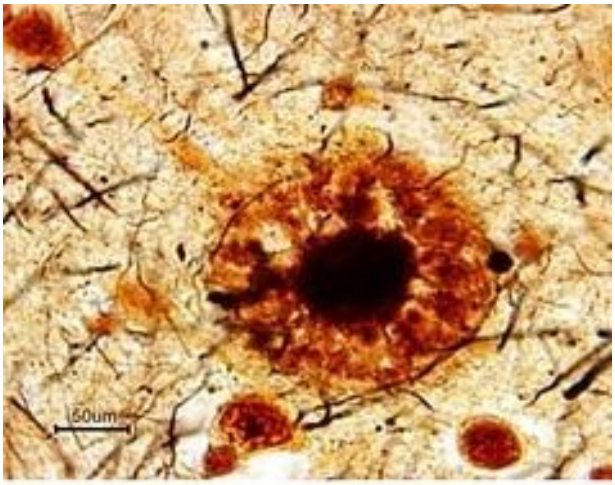

Figure 2. Neuritic plaques[20]