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 assessment 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 as Lytico-bodig disease¹, Meningioangiomatosis², subacute sclerosing panencephalitis³ (SSPE), Dementia pugilistica⁴, Pick’s disease⁵, Progressive supra nuclear palsy⁶, Ganglioglioma⁷, Argyrophilic grain disease⁸, Huntington’s disease⁹, Hallervorden-spatz disease¹⁰. Neuritic plaques are seen in Cerebral amyloid angiopathy¹¹, Temporal lobe epilepsy¹² 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.\(^{13}\)

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 (A\(\beta\), 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.

**DISCUSSION**

**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 ability 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.

DIFFERENTIAL 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) imaging16.
- 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 CSF18.
- Decreased fluorodeoxyglucose 18F (FDG) uptake on PET imaging in a specific pattern involving the brain’s temporo-parietal cortex19.

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 cortices16.

Recent Advances

Dr. Jie Xiang and colleagues from Taiyuan, University of Technology, China constructed 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 set21.

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 deterioration of network function across brain regions from healthy adults to those with mild cognitive impairment and AD21.

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 AD22.

The findings include evidence of how the protein fragments that make up Alzheimer’s plaque are deposited outside neurons and how loss of NEU1 possibly 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 mice22.

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 disease23.
1. It begins specifically in the lateral entorhinal cortex or LEC, which plays a major role in the consolidation of long-term memory
2. In long term, AD spreads from the LEC directly to other areas of the cerebral cortex, in particular, the parietal cortex
3. LEC dysfunction occurs when changes in tau and amyloid precursor protein (APP) co-exist

CONCLUSION

Alzheimer’s disease affects multiple areas of cognition and is characterized by a gradual onset with a slow, progressive decline. Neuritic plaques and neurofibrillary 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 2011 criteria 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


Colorado’s Dementia News & Research center.