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Biomarkers, ketone bodies, and the prevention of Alzheimer's disease

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ABSTRACT

Sporadic Alzheimer's disease (spAD) has three successive phases: preclinical, mild cognitive impairment, and dementia. Individuals in the preclinical phase are cognitively normal. Diagnosis of preclinical spAD requires evidence of pathologic brain changes provided by established biomarkers. Histopathologic features of spAD include (i) extracellular cerebral amyloid plaques and intracellular neurofibrillary tangles that embody hyperphosphorylated tau; and (ii) neuronal and synaptic loss. Amyloid-PET brain scans conducted during spAD's preclinical phase have disclosed abnormal accumulations of amyloid-beta (Aβ) in cognitively normal, high-risk individuals. However, this measure correlates poorly with changes in cognitive status. In contrast, MRI measures of brain atrophy consistently parallel cognitive deterioration. By the time dementia appears, amyloid deposition has already slowed or ceased. When a new treatment offers promise of arresting or delaying progression of preclinical spAD, its effectiveness must be inferred from intervention-correlated changes in biomarkers. Herein, differing tenets of the amyloid cascade hypothesis (ACH) and the mitochondrial cascade hypothesis (MCH) are compared. Adoption of the ACH suggests therapeutic research continue to focus on aspects of the amyloid pathways. Adoption of the MCH suggests research emphasis be placed on restoration and stabilization of mitochondrial function. Ketone ester (KE)-induced elevation of plasma ketone body (KB) levels improves mitochondrial metabolism and prevents or delays progression of AD-like pathologic changes in several AD animal models. Thus, as a first step, it is imperative to determine whether KE-caused hyperketonemia can bring about favorable changes in biomarkers of AD pathology in individuals who are in an early stage of AD's preclinical phase.

1. Introduction

Sporadic Alzheimer's disease (spAD) is the most common cause of dementia in the United States, being responsible for 60% to 80% of dementia cases [1]. Viewed from a temporal perspective, the illness can be divided into three successive phases [2]: (i) pre-clinical (pcAD), which is asymptomatic; (ii) mild cognitive impairment (MCI); and (iii) dementia (ADd). The three phases and the presumptive biomarker trajectories that accompany them [3] are modeled in Fig. 1.

The principal histopathological features of spAD include (i) extracellular cerebral amyloid plaques, consisting largely of aggregates of amyloid-beta (Aβ), cerebral amyloid angiopathy, intracellular neurofibrillary tangles (NFTs), which embody abnormally phosphorylated tau protein (p-tau) in the form of paired helical and straight filaments [4], and glial responses;

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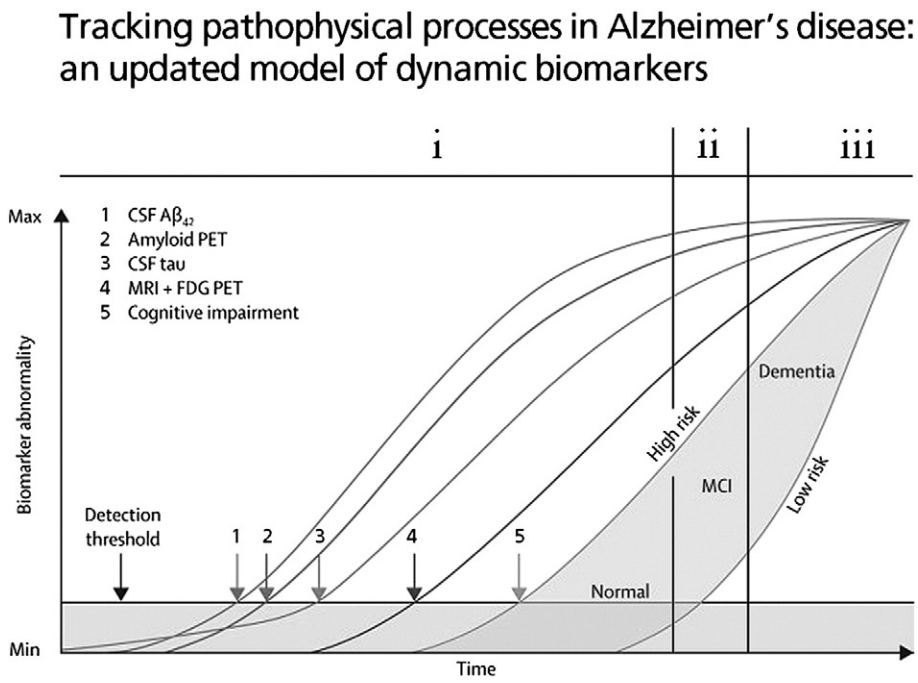

Fig. 1 – Evidence of Aβ42 abnormality is detected in the cerebrospinal fluid (curve 1) early in Phase i [preclinical phase]. Next, accumulation of amyloid deposits in the brain is disclosed by amyloid-PET scanning for amyloid content (curve 2). At the same time abnormalities of tau and phosphorylated tau (p-tau) may be detectable in the CSF (curve 3). In Phase i and during Phase ii (mild cognitive impairment [MCI]), selective decreases of the brain's glucose metabolism (cerebral metabolic rate of glucose [CMRglu]) have been demonstrated by FDG-PET(curve 4). CMRglu reduction may occur many years (even decades) before cognitive deterioration emerges in *APOE* ε4-positive and other high-AD-risk individuals. Independently, structural magnetic resonance imaging (sMRI) studies (also in curve 4) show atrophy of key areas of the brain concerned with memory and cognition, such as the hippocampus. Cognitive performance is designated by curve 5, which includes the shaded area under the curve. By the time the Phase iii [dementia] appears, cerebral deposition of Aβ (curve 2) will have slowed or ceased. Thus, in Phase iii, the rate and severity of memory loss, loss of executive function, and confusion, are better reflected by progressive changes in t-tau and p-tau, FDG-PET and sMRI. (Adapted from C.R. Jack, Jr., et al., Lancet Neurology 2013 [3]. Reproduced with permission from the publisher.)

and (ii) neuronal and synaptic loss [5]. For the most part, amyloid plaque builds up before cognitive deficits are identified, while neurofibrillary tangles, and neuronal and synaptic loss match progression of cognitive decline [3]. Over time, these brain lesions and accretions become extensive, and are associated with a seriously disrupted neuropil [5].

Tau proteins are expressed in 6 different isoforms in human adults, and belong to the category of microtubule-associated proteins (MAPS). Tau proteins are abundant in central nervous system (CNS) neurons. One of their important functions is to incorporate α- and β-tubulin monomers into neuronal microtubules (MTs) [6,7]. Thus, tau plays a major role in maintaining MTs in a state of dynamic stability. MTs direct specific membrane traffic in neurons and have recently been found to regulate dendritic spines—the major sites of excitatory synaptic input. MTs systematically leave the dendritic shaft and enter dendritic spines, modulating spine morphology. Such alterations appear to make a major contribution to synaptic plasticity and help maintain and control synaptic activities involved in memory formation and cognitive functions [8]. An insufficiency of synapses appears to be responsible for the memory impairment manifested in early AD [9]. Inhibition of α-tubulin deacetylase (HDAC6) activity has been reported to promote microtubule stability [10]. However, when tau becomes abnormally hyperphosphorylated (p-tau), as occurs in AD, its ability to support microtubule integrity is lost and the tubules deteriorate. The outcome of this disruptive process is the increasing synapse deficit and accumulation of insoluble aggregates of NFTs, hypothesized to play a major role in the causation and progression of AD [11].

2. Sporadic AD's predementia phases

2.1. *Preclinical spAD*

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) developed diagnostic guidelines for spAD and, in particular, pcAD. Three preclinical stages were proposed: (i) asymptomatic amyloidosis; (ii) asymptomatic amyloidosis + neurodegeneration; and (iii) amyloidosis + neurodegeneration + subtle cognitive decline [2]. The pcAD workgroup stressed the importance of examining the factors that best predict the risk of progression from normal cognition to MCI and ADd. To this end, the need to conduct longitudinal studies in spAD endophenotypes was emphasized [12].