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Biomarkers and evolution in Alzheimer disease

Stanley I. Rapoport[a,*] and **Peter T. Nelson**[b]

[a]Brain Physiology and Metabolism Section, National Institute on Aging, National Institutes of Health, Building 9, Room 1S-126, Bethesda, MD 20892, USA

[b]Department of Pathology, Division of Neuropathology, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, 40536, USA

Abstract

Brain regions and their highly neuroplastic long axonal connections that expanded rapidly during hominid evolution are preferentially affected by Alzheimer disease. There is no natural animal model with full disease pathology (neurofibrillary tangles and neuritic amyloid plaques of a severity seen in Alzheimer's disease brains). Biomarkers such as reduced glucose metabolism in association neocortex, defects in long white matter tracts, RNA neurochemical changes, and high CSF levels of total and phosphorylated tau protein, which are helpful to identify MCI and preclinical Alzheimer disease patients, may also provide insights into what brain changes led to this disease being introduced during hominid evolution.

Keywords

Alzheimer; Evolution; Brain; Biomarker; Association; Cortex; Metabolism; Neuroplasticity

1. Commentary

Despite the recent rapid accumulation of knowledge about the genetics and mechanisms of Alzheimer disease (AD), and the creation of transgenic mouse models of AD, at present there is no complete animal model for AD (Ashe and Zahs, 2010) nor any FDA approved truly disease-modifying drug available. Frustration based on these limitations is palpable in this volume, especially in view of early expectations of effective therapy based on the amyloid hypothesis, which have not been born out (Fleisher et al., 2008; Holmes et al., 2008). We may need new paradigms concerning disease pathogenesis and progression to develop more targeted agents, and the ability to test these agents during the pre-dementia mild cognitive impairment (MCI) or even earlier in cognitively intact individuals at risk (Reiman et al., 2004; Snowdon et al., 2000). This special issue on "Biomarkers for Neurodegenerative Disorders" provides up-to-date insights by experts on which biomarkers might be most useful for identifying factors disturbed in MCI and AD, for the differential diagnosis of AD, and for evaluating drug efficacy in the disease.

*Corresponding author. Tel.: +1 202 966 7355; fax: +1 201 496 1765. sir@helix.nih.gov (S.I. Rapoport).

AD as the cause of a dementia must be confirmed by postmortem evidence of brain accumulation and distribution of senile (neuritic) amyloid plaques (SPs) containing condensed β-amyloid peptide, and of neurofibrillary tangles (NFTs) consisting of paired helical filaments of phosphorylated tau protein. Using this definition, we might step back and consider aspects of AD related to brain evolution that are not emphasized in this biomarker volume.

AD appears to be a uniquely human disease, since comparable levels of SPs plus NFTs have not been identified in brain in any natural animal model, although transgenic manipulation with human genes has produced selective AD-like changes in rodents (Ashe and Zahs, 2010). Human uniqueness may be related to the fact that AD neuropathology, but particularly the NFTs (Braak and Braak, 1996), is concentrated in certain brain regions with long axonal connections, which the fossil record and comparative neuroanatomy (Stephan, 1983) suggest selectively expanded during primate but particularly hominid evolution, by a process termed “integrated phylogeny” (Rapoport, 1990). These regions include association neocortex and parts of the entorhinal cortex, amygdala (basolateral nuclear group), hippocampal formation (CA1 region and subiculum) and nucleus basalis of Meynert, with which the association cortex formed new connections. High CSF levels of tangle-related total tau protein and phosphorylated tau in MCI and AD are consistent with this evolutionary history for regional vulnerability to AD (Hampel et al., 2010). Further, the evolution of the native structure of tau proteins could be partly responsible for the interspecies differences in vulnerability to developing NFTs (Nelson et al., 1996).

During postnatal and adult human development, the cycles of myelination in different regions of the brain are consistent with their differential expansion during primate evolution, with some cortical regions of the AD-vulnerable telencephalic system myelinating beyond 30 years of age (Braak and Braak, 1996; Yakovlev and Lecours, 1967). In this regard, in late childhood (7–11 years), the thickness of primary sensory and motor cortex peaks before thickness of secondary association and polymodal association areas (Shaw et al., 2008), consistent with the principle integrated phylogeny. The peaks can be influenced by environment, intelligence and genetic factors, possibly genes that underwent positive selection during hominid evolution. These include the *ASPM* (abnormal spindle-like microcephaly associated) and *MCPH1* (microcephaly, primary autosomal recessive) genes (Evans et al., 2004a, b; Gilbert et al., 2005). Gene selection during hominid evolution may have introduced vulnerability of the telencephalic system to AD degeneration (Rapoport, 1989).

The relevance of the evolutionary and developmental data can be linked to the biomarkers that are discussed in this volume. For example, resting state FDG PET confirms the selective vulnerability of association compared with primary neocortex to AD, and can predict the late appearance of specific cognitive deficits. Reductions in the resting state regional cerebral metabolic rate for glucose ($rCMR_{glc}$) are more closely related to pathology involving NFTs than SPs (DeCarli et al., 1992; Hatanpaa et al., 1996, 1998). In cross-sectional studies, $rCMR_{glc}$ was reduced in diagnosed AD patients in relation to dementia severity. The reductions were more severe in neocortical association areas than in primary visual, auditory and somatosensory areas, even after correction for brain atrophy, whereas thalamic and basal

ganglia nuclei not belonging to the vulnerable telencephalic system were relatively spared (Kumar et al., 1991). Consistent with these observations, correlation analysis of $rCMR_{glc}$ data showed reduced functional interactions between neocortical association regions having long intrahemispheric and interhemispheric axonal connections in AD compared with control subjects (Horwitz et al., 1987). These correlational changes have since been related to atrophy and water changes in the relevant white matter tracts (Teipel et al., 1999), and suggest that AD symptoms can reflect functional disconnection involving long association pathways (Morrison et al., 1990).

The predictive value of regional FDG PET as a biomarker for later appearing cognitive deficits was demonstrated in several ways. In diagnosed AD patients having only a memory deficit, a lower right-than left-sided $rCMR_{glc}$ predicted the later (1–3 years) appearance of worse scores on language tests (e.g. Syntax Comprehension) than on visual spatial tests (e.g., Range Drawing), and *vice versa*, consistent with functional localization principles (Luria, 1973). Similarly, early appearing abnormal frontal/parietal association cortex metabolic ratios predicted later-appearing deficits in cognitive functions considered mediated by the frontal and parietal lobes (Grady et al., 1988; Haxby et al., 1990). In addition to resting state measurements, graded cognitive or behavioral tests with PET or fMRI can be employed during drug modulation to evaluate synaptic integrity and neurotransmission in pre-dementia and demented subjects (DeKosky et al., 1996; Furey et al., 1997; Mentis et al., 1998).

The concept of metabolic perturbations that precede pathology (much less detectable clinical symptoms or decreased cognitive test scores) raises the question of how we define AD, and for what we are seeking biomarkers. Are the biomarkers surrogates or predictors of future cognitive impairment? There are many highly prevalent potential comorbid diseases, including frontotemporal lobar degeneration, hippocampal sclerosis, and α-synucleinopathies, which are impactful non-AD neurodegenerative diseases (Nelson et al., 2010). Like AD, most of these are essentially human-specific, but each can cause cognitive impairment. Cerebrovascular disease is another multi-mechanism process that is nearly ubiquitous in late life and can cause both hypometabolism and cognitive decline.

A biomarker that seeks to link to a tailored neurotherapeutic agent would need to be specific to AD itself, rather than just hypometabolism or cognitive impairment. The future hence will require us to develop methods that are specific surrogates or predictors of pathology, but the pathology of interest is not merely “synaptic loss”, hypometabolism, or nonspecific “aging” pathways. Instead, we need to learn more about those specific pathways that correlate with SP and NFT development. These requirements indicate a need for greater understanding of the very complex human nervous system including the brain’s still-mysterious underlying genomic regulation (Nelson and Keller, 2007). This understanding must incorporate “evo–devo” mechanisms at the nexus of developmental and evolutionary biology (Zollikofer and Ponce de Leon, 2010).

One area where evo–devo research has been especially active is in the fields of neurobiology and RNA biochemistry (Kosik, 2009). RNA neurochemistry may in the future have special relevance to evolutionary biology, AD biomarkers, and AD neurotherapeutics. RNA

mechanisms have been hypothesized to be “complexity multipliers” that allow the ~10^5 genes expressed in the human brain to code for the brain’s ~10^{16} synapses—approximately 100 billion synapses per gene (Nelson and Keller, 2007). Special emphasis has been placed on non-coding RNAs in neurodegeneration (Hebert and De Strooper, 2009). MicroRNAs (miRNAs) are a biologically potent subset of the many non-coding RNAs, and their evolution has been active in primates and may have helped to augment the complexity of the human brain. Not only have miRNAs been shown to be aberrantly regulated in AD, but also this regulation has been implicated in AD pathogenesis (Wang et al., 2008). miRNAs have been tested in AD cerebrospinal fluid as a putative biomarker for the disease (Cogswell et al., 2008), and the search is on for other RNA-based potential diagnostic and therapeutic strategies (Ho et al., 2010).

We might speculate on how evolutionary principles involving the vulnerable telencephalic brain system can inform our understanding of AD mechanisms. One suggestion is that this more recently evolved system is highly neuroplastic (neurons can acquire new synaptic connections by axonal sprouting and other process) and particularly responsive to environment and to internal factors such as attention and ideation (Rapoport, 1999). Its high neuroplasticity may arise from selective alterations in its cytoskeletal components (Di Patre, 1991), or from other factors. A high level of neuroplasticity that is retained in late life, consistent with the concept of “cognitive reserve” (Stern, 2002), was evoked to account for reports that behavioral or cognitive intervention reduced cognitive decline in MCI and diagnosed AD patients (Buschert et al., 2010).

Brain evolution in primates may have been facilitated by heritable differences in neuroplasticity (Rapoport, 1999). These differences would have been exploited through natural selection when a relatively isolated population was presented with a new cognitively or behaviorally demanding milieu, extending the genes of individuals who responded best to the new demands within the population. Supporting this mechanism is *in vivo* imaging and direct recording evidence that association neocortex can be activated by attention or ideation alone, in the absence of a sensory or motor contribution (Kosslyn et al., 1995; Maunsell, 1995), and that activation of neuroplastic networks can promote and stabilize them for greater adaptive efficacy (Rapoport, 1999).

A high level of neuroplasticity in the brain association areas may increase remodeling of synaptic membranes and formation of β-amyloid, leading to pathology in genetically at-risk subjects. Maximum stability of membrane lipids occurs at 37 °C in homeotherms (Ginsberg et al., 1991). This “critical temperature” holds for different regions of the normal human brain and for primary cortex and cerebellum of the AD brain. However, the critical temperature is reduced in association cortex of the AD brain, suggesting increased membrane breakdown, resynthesis and energy consumption (Ginsberg et al., 1993). The reduced critical temperature may be caused by a reduced concentration of choline plasmalogen, an ether phospholipid that participates in myelin and synapse formation (Igarashi et al., 2011).

In the future, biomarkers of brain lipid structure and metabolism might help to assess lipid changes associated with the critical temperature reduction and other pathological processes

in the AD brain. These biomarkers could include the measurement of brain arachidonic acid metabolism with PET and of CSF prostanoid concentrations, both of which are increased in AD in association with neuroinflammation (de Leon et al., 2007; Esposito et al., 2008). Neuroinflammation and upregulated arachidonic acid metabolism contribute to AD and other progressive brain diseases (Basselin et al., 2011; Kim et al., 2009; McGeer and McGeer, 2003), and should be examined in detail.

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