Background – Insights from Neurodegenerative Disease for a Developmental Disorder

Alzheimer’s Disease (AD) is a progressive and fatal neurodegenerative disorder manifested by cognitive and memory deterioration along with progressive impairment of activities of daily living (1). Disease progression often starts 15-20 years prior to the appearance of clinical symptoms, thought to be initiated by the abnormal accumulation of amyloid-β (Aβ) in various areas of the brain (the ‘Amyloid Cascade Hypothesis’). Over time, this is followed by the appearance of neurofibrillary tangles, gray matter volume reductions and generalized brain morphometric changes (e.g., cortical atrophy, ventricular enlargement).

Adults with Down syndrome (DS) are at exceptionally high risk for AD. Virtually all adults with DS have neuropathological changes consistent with AD by age 40, including deposition of β amyloid peptide (Aβ) in diffuse and neuritic plaques, and most will develop clinical dementia by their late 60s (2). The high risk for AD has been attributed, at least in part, to triplication and overexpression of the gene for amyloid precursor protein (APP) on chromosome 21, leading to elevated levels of Aβ peptides. However, there is wide variation in age at onset of dementia, ranging from under 40 to over 70 years of age. With the development of PET radiotracers, such as Pittsburgh Compound B ([C-11]PiB) and Florbetapir ([F-18]AV45), researchers have been able to examine amyloid deposition in the living brain. The first papers documenting the appearance of beta amyloid in the brains of adults with DS were published
within the past decade (3, 4). Subsequent cross-sectional studies of moderate sized cohorts of individuals with DS confirmed that most adults with DS had significant amyloid deposition by their early 40’s, with some individuals showing “amyloid positivity” in their early 30’s (5).

**Advances – Treatment Trials in AD to Prevention in DS?**

Despite almost 20 years of research examining possible treatment options for AD, we have yet to have a ‘cure’ for this highly prevalent disease. Studies have focused on a wide range of approaches to AD, including interventions that target Aβ, tau, and various neurotransmitters, to name but a few. To date, none of these trials has been successful in reversing or preventing AD symptoms. Many researchers hypothesize that this is because the majority of studies have limited enrollment to individuals diagnosed with AD. Consequently, treatment aimed to address the effects of 15-20 years of neurodegeneration are unlikely to have a significant impact on functioning or disease course. Instead, the field’s recent focus has been on treating individuals at prodromal stages of AD, those who are at high-risk for dementia, but are not currently exhibiting symptoms. Hence, there are current prevention trials targeting populations with dominantly inherited forms of AD as well as with individuals with the ApoE4 gene (a gene variant linked to AD). As the majority of adults with DS will develop AD by their late 60’s, the DS population also offers a unique opportunity to examine the efficacy of drugs designed to prevent AD. In fact, at least two DS clinical trial networks are currently in the formative stages of development.

The National Institute on Aging (NIA) and the National Institute of Child Health and Human Development (NICHD) have come together to fund one of the largest longitudinal studies of AD in the DS population. Called the ABC-DS (Alzheimer’s Biomarker Consortium-Down Syndrome), the aims of this consortium have been to document the progression of the hallmark biomarkers of AD in DS (amyloid and neurofibrillary pathology and
neurodegeneration), identify biomarkers that best predict the 3-5 year onset of MCI-DS and dementia in the DS population, identify and characterize genetic factors that are associated with longitudinal DS phenotypes related to AD, and examine novel biomarkers useful for identifying subpopulations most likely to benefit from different approaches to treatment along with biomarkers specific to response to these treatments. The ABC-DS currently comprises 7 University-based sites: The University of Pittsburgh, the University of Wisconsin-Madison, Massachusetts General Hospital, Columbia University/IBR, the University of California-Irvine, and Washington University. The consortium has already enrolled approximately 400 adults with DS who are seen for evaluation every 16 months. including completing collection of data including neuropsychological assessment, caregiver questionnaires (on functioning and AD symptoms), blood (for genetic, lipidomic and proteomic analyses), MRI and PET scans (including amyloid, Tau, and FDG).

Outlook – Findings and Next Steps

Some initial findings suggest that episodic memory may be among the most sensitive neuropsychological measure indicating changes in functioning associated with amyloid deposition (5). A primary feature of amyloid-B plaque deposition in the DS population is the early elevated $[^{11}\text{C}]\text{PiB}$ binding in the striatum (6). Regions of interest most affected include the precuneus, striatum and anterior cingulate, findings similar to those with dominantly inherited forms AD. Longitudinal findings suggest that increased global Aβ is related to decline in verbal episodic memory, visual episodic memory, executive functioning, and fine motor processing speed, suggesting that Aβ accumulation may be a contributor to or biomarker of declining cognitive functioning in preclinical AD in DS (7).
The ABC-DS Consortium plans to complete its longitudinal work, including increasing the size of its network and the number of DS participants. In addition, it hopes to develop a set of predictive biomarkers for AD in DS and to develop more standardized assessment tools for the population. Finally, the consortium hopes to contribute to the development of prevention and treatment trials. The results of these trials are anticipated to help both adults with DS as well as the general population.
References