**Symposium Title:** Advancing Research on Alzheimer’s Disease in Down Syndrome: Insight into Early Detection and Characterization of Neuropathological and Cognitive Features

**Chair:** Sigan L Hartley¹

**Discussant:** Anna Esbensen²

**Overview:** Down syndrome (DS) is a neurodevelopmental disability most commonly caused by the complete triplication of chromosome 21 and is estimated to occur in 1 in 691 live births (Parker et al., 2010). Adults with DS have a heightened risk of Alzheimer’s disease (AD). Virtually all adults with DS evidence AD neuropathology in their 40s (Zigman & Lott, 2007) and 70-80% of adults with DS evidence clinical AD in their 60s and 70s (McCarron, McCallion, Reilly, & Mulryan, 2014). The heightened risk of AD in DS is thought to be due to the overproduction of brain β-amyloid, which is believed to occur as a result of the triplication of the gene coding for the amyloid precursor protein, located on chromosome 21. This high risk makes individuals with DS an important focus of research into AD cause(s), prevention and treatment.

This symposium is focused on recent research on the detection and neuropathological and cognitive characterization of AD in DS from projects such as the NIH/NIA funded Alzheimer’s Biomarkers Consortium of Down Syndrome (ABC-DS). The first presentation incorporates a data-driven approach to detecting mild cognitive impairment and dementia that takes into account the varying baseline functioning level of adults with DS. The second presentation examines the link between cerebrovascular neuropathology and AD in adults with DS, by drawing from autopsies of adults with DS with and without AD and those of young and old controls. The third study employs neuroimaging to characterize the accumulation of β-amyloid and tau during the preclinical stages of AD in DS. The final presentation profiles cognitive declines during the transitions from normative cognitive functioning to MCI and AD in DS drawing from multiple time points of data collection. Each presentation reflects a novel and meaningful contribution to the field. Together, findings have implications for the early detection of AD in DS and can help inform prevention and intervention efforts.

**References/Citations:**


¹University of Wisconsin-Madison, Waisman Center, Madison, WI

²Cincinnati Children’s Hospital, Cincinnati, Ohio
Title: Individual Differences in Lifelong Cognitive Abilities Must Be Considered For Staging MCI and AD-Dementia in Adults with Down Syndrome

Authors: Sharon J. Krinsky-McHale1,2, Joseph H. Lee2, Nicole Schupf2, Florence Lai3, H. Diana Rosas3, Ira Lott4, Christy Hom4, Margaret Pulsifer3, Wayne Silverman4

Introduction: Adults with Down syndrome are at increased risk for Mild Cognitive Impairment (MCI-DS; Krinsky-McHale & Silverman, 2013) and Alzheimer’s disease (AD-DS; Wisniewski et al., 1985). Triplication and overexpression of amyloid precursor protein (APP) contributes to this increased risk (Rumble et al., 1989). Complicating the picture is the fact that every phenotypic feature of Down syndrome shows a high degree of variability with respect to occurrence and degree of severity (Silverman, 2007). Lifelong cognitive impairments characteristic of adults with Down syndrome will perhaps obfuscate diagnosis of early clinical onset and progression of dementia. Therefore, “standard” assessment methods and diagnostic criteria are not applicable for this population. Efficient and accurate methods for assessment are needed, capable of taking into account variability in lifelong cognitive impairment.

Methods: We have examined the data of 134 individuals that are enrolled in the Biomarkers of Alzheimer’s Disease in Adults with Down Syndrome Study (Mage= 51.6± 7.2 yrs.). These participants span the mild to severe range of intellectual functioning. All participants received comprehensive evaluations at entry into the study. Following data collection, the dementia status of each participant was rated at consensus review which considered performance on a core neuropsychological test battery and clinical record review for each participant. Three groups were examined, Unaffected (N= 74, 55.2%), MCI-DS (N= 32, 23.9%), AD-DS (N= 28, 20.9%).

Results: We recorded premorbid functioning from participants’ medical records as a metric of lifelong cognitive functioning. Performance on our assessment battery was shown to be influenced not only by dementia status but also by degree of premorbid intellectual impairment. As an example, the pattern of results from the Cued Recall Test (measuring episodic memory) shows that level of premorbid intellectual functioning has potential for informing assessments of dementia status.

Discussion: Our study of older adults with Down syndrome illustrates the necessity of factoring in lifelong cognitive functioning when dementia status is being evaluated. The implication of this finding is that an alternative working definition of MCI-DS and AD-DS is needed that is referenced to individual decline rather than population-normed performance for biomarker studies, clinical trial outcomes and for early recognition of AD progression more generally.

References/Citations:

Acknowledgment:
This work was supported by funds from the New York State Office of people with Developmental Disabilities and NIH grant U01AG051412.
Title: Cerebrovascular Pathology as a Function of Age and Alzheimer Disease in Down Syndrome

Authors: Elizabeth Head¹, Frederick Schmitt¹, Ira Lott², Alex Helman¹

Introduction: People with Down syndrome (DS) due to full trisomy 21 develop Alzheimer disease (AD) neuropathology by 40 years of age (Head et al. 2016). AD in DS is thought to be driven primarily by the overexpression of the amyloid precursor protein on chromosome 21 and early deposition of beta-amyloid (Ab). Ab accumulates within extracellular plaques but also in association with the vasculature, known as cerebral amyloid angiopathy (CAA). We hypothesized that in DS, enhanced CAA (Head et al. 2017) may lead to more microbleeds (MB) in the brain. To test this hypothesis, we conducted an autopsy study of CAA and MB in the frontal and occipital cortex of people with DS.

Methods: Six autopsy groups were included in the study: 1) young controls (<40 years); 2) middle aged controls (40-60 years); 3) old controls (>70 years); 4) DS (<40 years); 5) DSAD (>40 years); 6) sporadic AD (>70 years). Fixed frontal and occipital cortex were sectioned at 50µm and immunostained for Ab1-40. Adjacent sections were stained with Prussian blue to visualize MBs. CAA was categorized as absent (0), mild (1), moderate (2) or severe (3) according to previously established studies (Biffi and Greenberg 2011; Boyle et al. 2015). MBs were counted using previously published methods (Wilcock et al. 2004).

Results: CAA was more extensive DSAD cases in the frontal and occipital cortex than that observed in sporadic AD and compared with age matched controls. MBs were also significantly higher in DSAD as compared with age matched controls but similar in DSAD to sporadic AD. In the occipital cortex, the presence of CAA was associated with MBs. In the frontal cortex, the number of MBs increased with increasing severity of CAA until the moderate stages and then leveled out. MBs were observed after age 30 years in occipital cortex in DS and rapidly increased after whereas in frontal cortex, MBs increased after 40 years of age.

Discussion: Cerebrovascular neuropathology may be a critical factor driving dementia in people with DS and may interact with AD neuropathology to lead to earlier ages of onset or more rapid progression. The success of future clinical trials to slow or prevent AD in DS may also need to consider the need to consider CAA and consequent MBs as targets.

References/Citations:
Paper Title: Neuroimaging Biomarkers in Down Syndrome

Authors: Karly A Cody1; Patrick J Lao1; Dana L Tudorascu2; Annie D Cohen2; Sigan L Hartley3, Peter D Bulova2, Rameshwari Tumuluru2, William E Klunk2; Benjamin L Handen2; Bradley T Christian1

Introduction: Down syndrome (DS; 1 in every 700 births1) arises from a triplication of chromosome 21, leading to an overproduction of amyloid precursor protein and an increased risk for early Alzheimer’s disease (AD). Nearly all adults with DS (by 40 years of age) demonstrate an elevated amyloid plaque burden.2 The study of the distribution and temporal spread of amyloid and tau in the brains of adults with DS is ongoing to advance understanding of the progression of AD-related neuropathology. Imaging amyloid burden and the subsequent neurodegeneration in the DS population in vivo will lead to better understanding of the AD pathophysiological process and aid in the development of earlier, more effective treatments in both DS and general populations.

Methods: The initial natural history study consisted of 68 nondemented adults with DS aged 30-53 years old. Subjects underwent Pittsburgh compound B (PiB) positron emission tomography (PET) and magnetic resonance imaging scans as well as neuropsychological testing at baseline and subsequently thereafter on 2-3 year intervals. Thresholds for PiB (amyloid) positivity [i.e., PiB(+)] were defined using cortical and striatal PiB SUVRs. Recently, the study expanded (Neurodegeneration in Aging Down syndrome, NiAD) to a larger sample size (n = 162 to-date), adding more recruitment sites and including an AD-related neuroimaging biomarker, AV1451 tau PET.

Results: PiB(+) was observed in about 23% of subjects in the natural history study. PiB(+) increased with age, with 50% of subjects >45 years showing significantly elevated PiB retention. The anterior ventral striatum showed the greatest and most prevalent age dependent increases in PiB deposition, followed by the precuneus, parietal and anterior cingulate. Longitudinally, rates of amyloid accumulation increased across all subjects, but were highest for subjects converting from PiB(-) to PiB(+). Recently acquired tau PET scans on these and the additional subjects from NiAD displayed a pattern of elevated tau burden in PiB(+) subjects compared to PiB(-) subjects.

Discussion: In DS, AD-related neuropathology is observed at an earlier age than the non-DS population. The striatal first spread of amyloid throughout the brain in DS mirrors the spread of amyloid in autosomal dominant AD. Additionally, the pattern of elevated tau burden in PiB(+) subjects is consistent with Braak staging seen in sporadic AD. Longitudinal neuroimaging to further characterize the temporal and spatial patterns of AD-related neuropathology is ongoing.

References:

Acknowledgments:
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1 University of Wisconsin, Waisman Center, Madison, WI; 2 University of Pittsburgh, School of Medicine and Public Health

Title: Cognitive Declines Associated with Mild Cognitive Impairment and Alzheimer’s Disease in Adults with Down Syndrome

Authors: Sigan L. Hartley1, Benjamin Handen2, Iulia Mihaila1, Patrick Lao1, Karly Cody1, William Klunk2, Dana Tudorascu1, & Bradley Christian1

Background: Adults with Down syndrome (DS) have an increased prevalence and early onset of Alzheimer’s disease (AD), purportedly due to the overproduction of brain β-amyloid resulting from the triplication of chromosome 21. Research on both the general and DS (e.g., Lao et al., 2016) populations has shown that accumulation of brain β-amyloid begins years to decades before the onset of clinical AD. During this transitional period, adults progress from normative cognitive functioning to mild cognitive impairment (MCI) and eventual AD. There is a need to understand the sequence of cognitive declines during these transitions. We will present data on the profile of cognitive declines associated with MCI and AD in an ongoing longitudinal study of adults with DS.

Method: Data was collected through the ongoing Neurodegeneration in Aging Down syndrome (NiAD) project. To-date a total of 162 adults with DS have completed at least one time point of data collection. Adults with DS were predominantly White, non-Hispanic, 52% were male, and had an average age of 36.80 (SD = 7.61) at the first time point. Direct (Down Syndrome Mental Status Examination; Haxby, 1989) and caregiver-reported (Dementia Questionnaire for People with Learning Disabilities and National Task Group- Early Detection Screen for Dementia; National Task Group, 2013) measures of dementia symptoms were administered. An extensive neuropsychological battery focused on episodic memory, language, executive functioning, visuospatial processing, and fine motor skills was also given. Participants underwent magnetic resonance imaging (MRI) scans and positron emission tomography (PET) scans using the imaging agent [11C] Pittsburgh compound B (PiB) and the AV-1451 Tau PET.

Results: Rate of decline in neuropsychological measures across the time points varied as a function of chronological age. On average, decline in cognitive functioning started in the 40s, becoming more marked in the 50s for episodic memory, working memory language (both expressive and receptive), adaptive living, motor coordination and planning, and visuospatial construction (unstandardized estimate = -0.68 to -3.68, p <.05). To-date, 12 adults with DS received a classification of AD and 11 received a classification of MCI. Declines in direct measures of visual and verbal memory, executive functioning, motor coordination, and executive functioning preceded classification of MCI and AD. PET β-amyloid and PET tau was associated with classifications of MCI and AD cross-sectionally.

Discussion: Better understanding of the transition from normal cognitive functioning to MCI and then AD is critical for guiding therapeutic trials for the prevention of DS population. Findings from the current study add to existing knowledge on the profile of cognitive declines associated with MCI and AD in the DS population.

References/Citations:


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1 University of Wisconsin-Madison
2 University of Pittsburgh School of Medicine and Public Health
3 University of Illinois at Chicago
4 Columbia University Medical Center