9-27-2021

Down Syndrome and Dementia:: A Patient and Care-Giver Centered Approach

Mary M. Stephens
Thomas Jefferson University

E. Adel Herge
Thomas Jefferson University

Charmaine Wright
ChristianaCare Center for Special Health Care Needs

Doi: 10.32481/djph.2021.09.016

Down Syndrome and Dementia:

A Patient and Care-Giver Centered Approach

Mary M. Stephens, MD, MPH, FAAFP, FAADM;[1] Eileen Herge;[2] Charmaine Wright, MD, MSHP[3]

1. Medical Director, Jefferson Continuing Care Program (JCCP); Clinical Lead, Christiana Care Down Syndrome Program; Associate Professor, Family and Community Medicine, Thomas Jefferson University

2. Occupational Therapist; Associate Professor CHP, Thomas Jefferson University

3. Medical Director, ChristianaCare Center for Special Health Care Needs; Medical Director, Mary Campbell Center, Adjunct Assistant Professor of Medicine

> *LG is a 49-year old woman with Down syndrome (DS). She and 3 other women with intellectual disability live in a house in Delaware. These four women are assisted in their activities of daily living by a small team of round-the-clock caregivers. LG used to need a little help with zippers but chose her outfit and dressed herself. She needed some assistance with food preparation but fed herself. Until early 2020, LG had spent the previous 10 years attending a daily morning gathering with fellow residents after eating a hearty breakfast. She loved pancakes and bacon. She was enthusiastic and friendly, often first to sit and the first to share the expected weather for the day. She played tennis two times a week and had done so for the past 20 years. In late 2019, LG started closing her eyes during morning program and wasn't the first to share the weather. She did not want to participate in tennis and was easily frustrated by putting on the shoes she had worn for several years, once throwing them across the room. Her balance was off and she had a fall at the courts. After checking her sleep apnea treatment, her thyroid function, her hearing and vision, LG was treated for depression. However, she started eating fewer pancakes at breakfast. She would hold food in her cheek for far too long and lost a small amount of weight as a result. She spoke much more quietly and often would shake her head yes or no when asked a question without a verbal reply. Her eyes were closed for much of the morning though she was awake.*

Both LG's family and health care team asked whether the changes we saw could all be from depression. What else could be going on and what would be LG's expected course? What workup and management should follow? We considered Alzheimer's dementia. Down syndrome (DS), caused by an extra copy of the twenty-first chromosome, is a significant risk factor for early onset Alzheimer's dementia (AD). The mechanism is believed to be linked to overproduction of amyloid precursor protein (APP) linked to the extra copy of the twenty-first chromosome, with subsequent development of amyloid plaques and neurofibrillary tangles in the brain.[1] Given the increase in lifespan for individuals with DS from the mid 20's in the 1980s to 60 today, the number of older Americans with DS is increasing and members of the health care team need to better understand the unique characteristics of these individuals in order to optimize best practices for care.[2,3] We will review common characteristics and co-morbidities of individuals with DS, review the epidemiology of AD and clinical presentation of AD in this cohort, discuss practical considerations for diagnosis and treatment as well as strategies to maximize support for caregivers. Consistent with the National Plan to Address Alzheimer's

Doi: 10.32481/djph.2021.09.016

Disease, we will focus on the importance of the early detection of AD and what it means to patients, caregivers, and the healthcare system.

Down Syndrome

DS is the most common genetic cause of intellectual disability (ranging from mild to severe) and is associated with a number of common medical conditions including hypothyroidism, sleep apnea, vision and hearing abnormalities, seizure disorders, dental disease, autism, and mental health issues.[3,4] The first evidence-based guidelines for adults with DS were only recently published and provide guidance on best practices for care of this vulnerable population, and also highlight the need for further research given the limited quality of the available evidence.[2] The strongest recommendation from the guidelines is a strong recommendation to screen adults with DS for AD beginning at age 40 with a dual purpose of identifying AD along with potentially treatable medical conditions that may appear to be AD or contribute to functional decline.[2] It is estimated that approximately 30% of adults with DS in their 50s and 50% of those in their 60s have AD. The average age for AD diagnosis in DS is 55. Clinical AD appears to be rare in individuals with DS prior to the age of 40, and experts urge caution in making a diagnosis prior to this age.[2,3]

What Does AD Look Like in Patients with DS?

While some experts suggest that the later stages of AD in people with DS are similar to the general population of people with AD, the early stages of AD in DS are very variable.[5] In a recent systematic review, “frontal-like symptoms” such as changes in fearfulness, lack of energy, withdrawal, disinhibition, and sadness were cited as the most common presentation of AD in people with DS. Changes in memory were reported less consistently. This may be in part due to baseline impairments in working memory in individuals with DS related to function of the hippocampus versus universal decline in working memory skills as a part of “normal” aging in DS. Gait dyspraxia (difficulty initiating walking or making turns, shuffling, fear and avoiding of obstacles such as stairs) and new onset seizures can be early markers of cognitive decline.[6]

Diagnosing Mild Cognitive Impairment (MCI-DS) and AD in Patients with DS

The most commonly used screening tool for evaluating the early indicators of dementia in DS is the National Task Group – Early Detection Screen for Dementia (NTG-EDSD).[7] The instrument contains both signal items associated with an increased risk of AD (unexpected problems with memory, getting lost, gait changes, new seizures, confusion in familiar settings, personality change) and 51 questions in six cognitive or functional domains - Activities of Daily Living (ADL), Language, Sleep-Wake Change Patterns, Ambulation, Memory, and Behavior and Affect. In evaluating the sensitivity of the NTG-EDSD specifically for the detection of MCI-DS, the authors highlight some of the difficulties in using the instrument clinically, which include a lack of consensus with respect to the diagnostic criteria for MCI-DS beyond a decline in cognitive abilities worse than expected for age, and for AD in DS in general since there are a lack of population-based standards.[7] The NTG-EDSD scoring scale helps clinicians compare patients with DS to their own baseline as the questions are scored always been the case, always but worse, new symptom in the past year, or does not apply. The framework of analysis reflects transitions from “clinically stable” to concern for MCI-DS to suspicious for AD.

One or more new concerns in the domains of Language and Memory appear to distinguish individuals who are cognitively stable vs. those with probable early AD (Sensitivity = 0.895 and Specificity = 0.802) or MCI-DS (Sensitivity = 0.806 and Specificity = 0.802).[7] In practical terms for the busy clinician, the authors of this study suggest that the likelihood is extremely high that an individual with five or more concerns in the domains of Language and Memory has MCI-DS or AD and is high if there is at least one concern. In contrast, those with no concerns in the Language and Memory domain or few concerns overall or in signal items have a low likelihood of MCI-DS or AD. Using a criterion of five or more concerns overall, the study found a sensitivity of 0.868 for dementia (vs 0.417 for MCI-DS) with a specificity of 0.802.[7]

Clinical Evaluation in Aging Patients with DS

Annual assessment of thyroid function and periodic assessment for risk of sleep apnea are important in the lifespan care of individuals with DS. A decline in mean verbal IQ and decreased cognitive flexibility is seen in individuals with DS and untreated OSA.[8] In patients with DS where there are concerns for functional decline other conditions to consider are depression, anxiety, vision/hearing changes, Vitamin B12 deficiency, celiac disease, structural heart disease, seizure disorder, polypharmacy, diabetes, kidney disease, or urinary tract infection. Somewhat unique to individuals with DS is atlantoaxial instability (AAI) presenting as functional decline. In general, the risk of AAI is much higher in younger individuals than older individuals with DS but can present as change in gait, handedness, or functional decline. Individuals with DS may have difficulty expressing pain due to challenges with communication but this possibility should be explored. Validated scales for depression or anxiety do not exist for individuals with DS so clinicians have to be clinically suspicious and need to consider therapeutic trials as part of their diagnostic work up. Constipation is extremely common in individuals with DS and needs to be considered.

Treatment Strategies

Pharmacotherapy has shown little promise in the prevention or treatment of AD in patients with DS although the evidence is of low quality. Clinicians can consider a trial of medications to postpone expression of symptoms and to improve function slightly, but need to monitor for side effects.[9] Pharmacotherapy and non-pharmacologic approaches to treat co-existing depression and anxiety, and improve quality of life are important considerations in the care of patients with AD and DS. Cognitive enhancers such as donepezil or rivastigmine are the only drugs approved by the FDA for the treatment of AD investigated in individuals with Down syndrome (DS). Symptom specific therapy may be necessary if a patient is impulsive or aggressive; both stimulant and antipsychotic medications may be used on an “off-label” basis (based on evidence but not FDA indication) in low doses respectively.

Role of the Interprofessional Team in the Care of Patients with Known or Suspected MCI-DS or AD

Caring for and supporting patients with DS and MCI-DS and AD is best managed from an Interprofessional team approach to achieve the best outcomes.[10,11] Patients with DS and MCI-DS or AD may demonstrate changes in behavior, personality, emotional responses and/or affect as well as difficulty with familiar activities such as self-care or decreased participation in activities they used to enjoy as the condition worsens. This can be stressful for caregivers when strategies

that have been successful in supporting the patient with DS are no longer working.[12] Having a network of Interprofessional providers with expertise in addressing these changes can help families and caregivers prepare for "next steps," integrate adaptations to help the patient remain age in place and implement strategies to improve the quality of life for the patient and the caregivers.[13] Social workers, case managers, nurses and occupational therapists can evaluate the needs of the patient and caregiver and provide recommendations to support patient participation in activities and routines which can improve patient overall health and well-being as well as reduce unwanted behaviors. Several national resources are available to provider information and resources on best practices in supporting patients with DS and MCI-DS and AD. Closer to home, regional and local resources with expertise in supporting patients with DS can provide more specific consultation and support tailored to the individual patient and caregiver needs.

The role of primary care becomes apparent when health disparity is demonstrated.[14] As the mean age of survival for an individual with DS stretches to 60 years and beyond, the need for appropriate cancer screening is all the more relevant.[15] Those with intellectual and developmental disabilities (IDD) are not screened for breast, colon, prostate, and cervical cancer at the rates of their similar-aged peers without IDD. Thus, higher morbidity and mortality result. During the COVID-19 pandemic, those with IDD had higher risk of contracting, and also becoming sick and dying from the virus.[16] The goal of the primary care physician is to recognize and manage the medical and socioeconomic disparity that exists for patients with DS, especially as they age. In the case of patients with DS and dementia, understanding the living situation, who speaks for the individual when they cannot speak for themselves, recognizing the potential for injury and abuse—all while providing quality health care—takes an interprofessional team.

Emerging Research

The Alzheimer's Biomarkers Consortium – Down Syndrome (ABC-DS) is a NIH-funded research initiative to evaluate the effectiveness of biomarkers for both diagnosis and prognosis. PET Scan is being studied for its role in both diagnosis and prognosis. Amyloid PET is positive in nearly all individuals with DS by the age of 40 given the uniform presence of plaques and tangles, so is not helpful in diagnosis or prognosis, but Tau PET may play a role. In 2018, the NIH launched the INCLUDE project (Investigation of Co-occurring conditions across the Lifespan to Understand Down syndrome) which funds multiple studies to address general health and quality-of-life needs for people with DS. Improving baseline health status and inclusive health practices that address health disparities may have a protective role or delay the onset of clinically significant signs and symptoms of AD.

> *LG's NTG-EDSD was suspicious for AD. She was started on donepezil but had diarrhea that was not improved by diet, other medications, and changing the timing of administration. Her case manager was instrumental in engaging LG in one on one smaller activities and a nutritionist helped plan 4-5 mini meals a day which LG enjoys. Her weight has stabilized though she continues to pocket food and her diet was downgraded to a minced and moist consistency to make it easier to chew. She goes for a walk once a day with a walker, sometimes on the tennis courts. She keeps her eyes open when she is chair dancing; music and singing are the most effective treatments for her withdrawal and lack of verbal response. Though the pandemic decreased her opportunities for engaging in community activities outside of her home, at the time of this*

writing, she was enjoying her first live music experience with friends on a sunny patio in her town.

References

1. Millan Sanchez, M., Heyn, S. N., Das, D., Moghadam, S., Martin, K. J., & Salehi, A. (2012, March 1). Neurobiological elements of cognitive dysfunction in down syndrome: Exploring the role of APP. *Biological Psychiatry*, *71*(5), 403–409. PubMed https://doi.org/10.1016/j.biopsych.2011.08.016
2. Tsou, A. Y., Bulova, P., Capone, G., Chicoine, B., Gelaro, B., Harville, T. O., ... Whitten, M. S., & the Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome Workgroup. (2020, October 20). Medical care of adults with Down syndrome: A clinical guideline. *JAMA, 324*(15), 1543–1556. PubMed
3. Chicoine, B., Rivelli, A., Fitzpatrick, V., Chicoine, L., Jia, G., & Rzhetsky, A. (2021, April 19). Prevalence of common disease conditions in a large cohort of individuals with down syndrome in the United States. *Journal of Patient-Centered Research and Reviews*, *8*(2), 86–97. PubMed https://doi.org/10.17294/2330-0698.1824
4. Coppus, A. M. (2013). People with intellectual disability: What do we know about adulthood and life expectancy? *Developmental Disabilities Research Reviews*, *18*(1), 6–16. PubMed https://doi.org/10.1002/ddrr.1123
5. Lautarescu, B. A., Holland, A. J., & Zaman, S. H. (2017, March). The early presentation of Dementia in people with Down syndrome: A systematic review of longitudinal studies. *Neuropsychology Review*, *27*(1), 31–45. PubMed https://doi.org/10.1007/s11065-017-9341-9
6. Anderson-Mooney, A. J., Schmitt, F. A., Head, E., Lott, I. T., & Heilman, K. M. (2016, April). Gait dyspraxia as a clinical marker of cognitive decline in Down syndrome: A review of theory and proposed mechanisms. *Brain and Cognition*, *104*, 48–57. PubMed https://doi.org/10.1016/j.bandc.2016.02.007
7. Silverman, W., Krinsky-McHale, S. J., Lai, F., Diana Rosas, H., Hom, C., Doran, E., ... Schupf, N., & the Alzheimer's Disease in Down Syndrome (ADDS) Consortium. (2021, May). Evaluation of the National Task Group-Early Detection Screen for Dementia: Sensitivity to 'mild cognitive impairment' in adults with Down syndrome. *J Appl Res Intellect Disabil, 34*(3), 905–915. PubMed
8. Breslin, J., Spanò, G., Bootzin, R., Anand, P., Nadel, L., & Edgin, J. (2014, July). Obstructive sleep apnea syndrome and cognition in Down syndrome. *Developmental Medicine and Child Neurology*, *56*(7), 657–664. PubMed https://doi.org/10.1111/dmcn.12376
9. Prasher, V. P., & Prasher, M. (2016, December). Folate, vitamin B(12), Down syndrome and Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *31*(12), 1372–1373. PubMed https://doi.org/10.1002/gps.4519
10. Wranik, W. D., Price, S., Haydt, S. M., Edwards, J., Hatfield, K., Weir, J., & Doria, N. (2019, June). Implications of interprofessional primary care team characteristics for health

services and patient health outcomes: A systematic review with narrative synthesis. *Health Policy*, *123*(6), 550–563. PubMed https://doi.org/10.1016/j.healthpol.2019.03.015

11. Körner, M., Wirtz, M. A., Bengel, J., & Göritz, A. S. (2015, June 23). Relationship of organizational culture, teamwork and job satisfaction in interprofessional teams. *BMC Health Services Research*, *15*(1), 243–243. PubMed https://doi.org/10.1186/s12913-015-0888-y
12. Iacono, T., Bigby, C., Unsworth, C., Douglas, J., & Fitzpatrick, P. (2014, October 25). A systematic review of hospital experiences of people with intellectual disability. *BMC Health Services Research*, *14*(1), 505–505. PubMed https://doi.org/10.1186/s12913-014-0505-5
13. Jokinen, N., Janicki, M., Keller, S., McCallion, P., Force, L. T. and National Task Group on ID and Dementia Practices. (2013). Guidelines for structuring community care and supports for people with intellectual disabilities affected by dementia. *Journal of Policy and Practice in Intellectual Disabilities, 10*(1), 1–24.
14. Krahn, G. L., & Fox, M. H. (2014, September). Health disparities of adults with intellectual disabilities: What do we know? What do we do? *J Appl Res Intellect Disabil*, *27*(5), 431–446. PubMed https://doi.org/10.1111/jar.12067
15. Bull, M. J. (2020, June 11). Down Syndrome. *The New England Journal of Medicine*, *382*(24), 2344–2352. PubMed https://doi.org/10.1056/NEJMra1706537
16. Doody, O., & Keenan, P. M. (2021, December). The reported effects of the COVID-19 pandemic on people with intellectual disability and their carers: A scoping review. *Annals of Medicine*, *53*(1), 786–804. PubMed https://doi.org/10.1080/07853890.2021.1922743