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# Alzheimer's Disease in Adults with Down Syndrome

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## Introduction

Alzheimer's disease (AD) is quite common in individuals with Down syndrome and occurs at a younger age than in those without Down syndrome. However, diagnosing AD in individuals with Down syndrome is often challenging, and testing can be less precise. As a result, any time an individual with Down syndrome presents with a decline in skills, it is often incorrectly assumed the decline is due to AD. As described in the article [Decline in Skills and Behavioral Change](#), there are many mental and physical health conditions that can cause an adult with Down syndrome to decline, and a thorough assessment is indicated to optimize diagnosis and treatment. This article will focus on the unique aspects or features of AD in individuals with Down syndrome. AD in individuals with Down syndrome is sometimes abbreviated DS-AD, and that will be used in this article.

## Pathogenesis

The amyloid precursor protein (APP) gene is on chromosome 21 and, therefore, is triplicated in Down syndrome. There is compelling evidence that increased gene dosage of APP is necessary for DS-AD because individuals with Down syndrome carrying three copies of the APP gene are at markedly increased risk of developing this condition.<sup>1-3</sup> Though the data are limited, it appears that those rare individuals with partial trisomy, in which only two copies of the APP

gene are present, are not at increased risk of DS-AD. This realization informs the diagnostic approach to DS-AD and therapeutic efforts to prevent it.

Nearly all individuals with Down syndrome develop the neuropathological changes of AD in their brains by age 40<sup>4</sup>, and all do so by age 60.<sup>5-7</sup> These neuropathological changes precede symptom onset by 20 or more years. Factors that contribute to the development of DS-AD may include mitochondrial dysfunction and neuroinflammation.<sup>8</sup> In persons without Down syndrome, metabolic dysregulation due to insulin resistance may contribute to the development of Alzheimer's disease,<sup>9</sup> which some have called "Type 3 diabetes." The implications of this finding for individuals with Down syndrome are not known. Finally, sleep apnea may also be a risk factor as it is associated with a greater amyloid burden and small vessel pathology in DS-AD.<sup>10</sup> In individuals without Down syndrome, positional obstructive sleep apnea increases with age. However, the links between age, obstructive sleep apnea, and Alzheimer's disease require further investigation in individuals with Down syndrome.

## Incidence

Despite the prevalence of these brain changes, not all adults with Down syndrome develop clinical findings of Alzheimer's disease. Still, the incidence is higher than in individuals without Down syndrome, and the rate increases with age.<sup>11</sup> Between the ages of 35 and 49, an

estimated nine to 23 percent of individuals with Down syndrome develop symptomatic AD. Between 50 and 59 years, the cumulative incidence is estimated at 55 percent, and may be greater than 75 percent in those 60 years of age and above.<sup>12-15</sup>

Based on neuropathology, most dementia in persons with Down syndrome appears to be AD. However, other neuropathologies may be present, including those characteristic of synucleinopathies including Lewy bodies.<sup>16</sup> Motor changes suggestive of Parkinson's disease are uncommon.<sup>17</sup> Additional research is needed to clarify how pathologies other than those linked to AD contribute to the clinical picture of dementia in adults with Down syndrome.

## Age of Onset and Clinical Course

The average age at which the clinical development of AD is diagnosed in individuals with Down syndrome is 54 to 55 years of age.<sup>18-20</sup> Although individuals with Down syndrome are at high risk for developing symptomatic AD after age 40,<sup>21</sup> symptomatic onset before age 40 is considered uncommon. The life expectancy for a person with DS-AD is 57-60 years.<sup>18,20</sup> One study found that the median survival after diagnosis for men, 3.1 years, was shorter than that for women, 4.4 years. However, men were diagnosed 1.8 years later than women and, therefore, the age of death was comparable.<sup>20</sup> Alzheimer's disease is the

most common cause of death in adults with Down syndrome.<sup>22</sup>

## Symptoms

The earliest symptoms of DS-AD are mood and behavioral changes such as increased apathy, stubbornness, depressed mood, and aggressiveness.<sup>23-28</sup> Although memory impairment has been noted as an early indicator,<sup>29,30</sup> neuropsychiatric symptoms, as noted above, are more commonly described. Altered appetite, thirst, or unintentional weight loss may also be initial findings. One study in individuals with Down syndrome documented an annual 0.23 kg/m<sup>2</sup> loss in body mass index starting at age 36.5 years, with a greater loss being associated with greater beta-amyloid on PET scan.<sup>31</sup>

Other symptoms associated with DS-AD progression include sleep changes, decline in skills and increased seizure activity. Sleep changes may include day-night reversal, daytime fatigue, and disrupted nighttime sleeping. As the disease progresses, a variety of skills are lost including general mental functioning and self-care skills.<sup>22</sup> The earliest symptoms of skill loss may include the inability to perform multi-step tasks, the need for more prompts to complete certain tasks, or needing others to assist with task completion. Up to 84% of individuals with Down syndrome who develop Alzheimer's disease will also have seizures, a rate much higher than those affected by Alzheimer's disease without Down syndrome.<sup>32</sup> There may

be new onset of seizures or a change in type or pattern of existing seizures. There is a strong association of seizures with cognitive decline in individuals with DS-AD.<sup>33</sup>

Symptoms of advanced DS-AD include urine and/or stool incontinence, gait and balance changes, and dysphagia. The latter may manifest as choking, gagging, or coughing when eating or drinking, fear of eating, or aspiration pneumonia. Regrettably, dysphagia is often a major contributor to death in individuals with DS-AD.

## Screening

The [GLOBAL Medical Care Guidelines for Adults with Down Syndrome](#)<sup>34</sup> recommend screening starting at age 40 to assess the individual in the following areas:

- Cognition, memory, and executive function
- Behavior and personality
- Communication
- Adaptive functioning
- Ambulation and motor skills
- Any recent decline in established skills

A [screening questionnaire](#) is available through the National Task Group (NTG) on Intellectual Disabilities and Dementia Practices.

## Diagnosis

When assessing a pattern of decline consistent with DS-AD, an evaluation to rule out other causes is indicated. Many possible causes of decline are described in the article [Decline in Skills and Behavioral Change in Adults with Down Syndrome](#), so focusing on conditions more common in Down syndrome is beneficial. Despite ongoing research regarding biomarkers and imaging evaluations, there is no single, specific test that diagnoses any form of AD. Complicating matters, neuropsychological tests standardized for individuals without an intellectual disability can be misleading.<sup>35</sup> Tests designed for individuals with intellectual disabilities tend to be more accurate for individuals with Down syndrome, but it may be more difficult to find a qualified professional to complete the testing. Regular and recurrent assessments using appropriate tests can be particularly beneficial to assess the onset and progression of cognitive decline.<sup>36</sup>



## NTG-Early Detection Screen for Dementia (NTG-EDSD) Tool

### What

The NTG-EDSD is a tool to record changes in functional and cognitive abilities that occur as adults with an intellectual disability get older.

### Why

Designed to recognize changes in functioning early so they can be discussed with a healthcare professional.

### Where

The NTG-EDSD is available for free online at [www.the-ntg.org/ntg-edsd](http://www.the-ntg.org/ntg-edsd).

### How

Encourage individuals and families to fill out the NTG-EDSD form no later than age 40 and before changes are noticed to establish a baseline level. Repeat the form yearly. Consider adding a video of the adult with an intellectual disability doing three relevant tasks.

## Prevention

While there is some evidence regarding risk factors for AD in individuals without Down syndrome<sup>37-40</sup> similar studies have not been done for individuals with Down syndrome. In the absence of data, the following recommendations for possible prevention measures apply to everyone:

- Regular physical activity
- Dietary modifications such as the Mediterranean diet or DASH diet
- Hearing assessment and treatment
- Social engagement
- Engaging in intellectually stimulating games
- Stress management

As noted above, sleep apnea, which is more common in individuals with Down syndrome, has been associated with increased amyloid in DS-AD. Screening for and treating sleep apnea may benefit the quality of sleep and daily function and theoretically reduce DS-AD progression.

## Treatment of Symptoms and Seizures

There is no effective treatment for DS-AD. Cholinesterase inhibitors and memantine are often prescribed for symptoms, but research to date on these interventions is considered low quality, making it difficult to draw conclusions about their effectiveness.<sup>41</sup> Side effects of cholinesterase inhibitors include gastrointestinal upset and decreased appetite, whereas memantine can increase agitated behavior. Unfortunately, at this time the newer antibody-based medications (e.g. lecanemab) have not been examined for safety and efficacy in individuals with Down syndrome. Until more data are available on this target population, caution is advised.

The seizures seen in DS-AD may be of various types,<sup>28</sup> and medication selection is based on type of seizure, possible medication side effects, and the impact of the medication on other co-occurring health conditions. Myoclonic epilepsy is the most prevalent seizure type,<sup>42</sup> and the myoclonic jerking experienced by many with DS-AD is infrequent and not particularly bothersome to the individual. Prescribing anti-seizure medications in this situation can

cause more side effects than benefit. When the jerking is frequent and affects the hands, however, it can make it difficult for the person to eat. These seizure movements may also warrant treatment if they affect the trunk and/or legs causing loss of balance or are frequent enough to be bothersome or disturbing to the individual. Having a plan to care for breakthrough seizures is essential and providing rescue medications to the family or caregivers should be considered.<sup>43</sup>

## Caring for Someone with DS-AD

There are limited data on the caregiver approach to an individual with DS-AD, but several key ideas should be communicated to the care team. These include offering activities the person can still manage, encouraging health promotion, addressing triggers of negative behavior, and supporting general mental health.

## Activities

As the disease progresses, the person's capacity will decrease; however, even in advanced stages, individuals can still enjoy various activities. Often the pace of the activity will need to be slower, even if the person enjoyed faster-paced activities in the past. Early in the disease, there will be some fluctuation of skills and interests. What a person is capable of one day, he or she may not be the next, but may again later. Sometimes high-energy activities

may be enjoyed and keep the person engaged, but at another time may be overstimulating and contribute to a negative behavioral change. Overall, family and caregivers should be encouraged to continuously assess the person's needs and abilities and adjust accordingly. It is important to engage with the individual using effective communication strategies including making eye contact, talking slowly, and using gestures or images along with verbal communication.

## Health Promotion

As noted in the article [\*Health Promotion for Adults with Down Syndrome\*](#), health-promoting activities will not only optimize physical health but may also reduce the rate of cognitive and functional decline. By limiting the number of co-occurring health conditions, quality of life will increase, and negative behaviors can be minimized.

## Triggers of Behavioral Change

### Caregivers

Even with the best intentions, caregivers can trigger negative behaviors. For example, reasoning with a person who has a declining ability to reason is often unproductive. Short of an immediate safety issue (the person is doing or about to do something that is dangerous), in most situations, backing off, waiting a few minutes, and trying again is more likely to be successful and contribute to fewer behavioral upsets.

### Pain

Pain is a common contributor to a change in behavior. Painful medical conditions include infections (e.g., a bladder infection or pneumonia), metabolic conditions (e.g., diabetes, thyroid conditions), dehydration, gout, and/or inadequate sleep. Something as simple as cerumen impaction of the ear canal (a common ailment in individuals with Down syndrome) can cause reduced hearing or significant pain, with a corresponding impact on behavior and/or function. Oral disease can also cause pain that is difficult to detect.

### Environment

Extreme temperatures, bad smells, too much or too little light, excessive noise, and other factors can be stressful and result in a change in behavior. New environments may be challenging. For example, if an individual with Down syndrome attends a gathering at a new setting in the presence of many relatives that he or she has not seen for years, this environment may be too overwhelming, causing behavioral change or an emotional "shutdown". Even events that are much less hectic can be difficult to manage.

For individuals who do not live with family, sometimes visiting the family home is equally overwhelming. Their present residence is now familiar, and the family home—no matter how long the person had lived there—may no longer be remembered due to memory loss. If visiting the family home is too stressful, the family may need to visit the person in his or her home

instead. For an individual with DS-AD, leaving his or her environment to go into the community or to visit with less familiar people, especially in larger groups, may be frightening or upsetting.

## Mental Health

There are usually positive things in most environments that the individual did not find stressful prior to developing AD that can be highlighted and used to comfort the individual. For example, posters of favorite singers, a fluffy pillowcase, or a preferred snack may all be helpful. Additionally, caregivers can enhance the environment with appropriate supports. For example, putting the person's picture on their bedroom door, putting a picture of a toilet on the bathroom door, and similar interventions can help the individual feel less confused and reduce behavioral changes.

Music has been shown to be beneficial for individuals with Alzheimer's disease.<sup>44</sup> Using playlists of music that the person has enjoyed in the past may be calming, particularly if it is music associated with happy times. An individual with Down syndrome may particularly enjoy music from their youth, because distant memory tends to remain intact longer than short-term memory.

Wandering can sometimes be a problem that requires environmental changes. If the person is just wandering around the house, no intervention may be needed, but if they are wandering outside, some means of preventing that will be important for safety. Caregivers may

consider placing a GPS locator in the person's clothing to allow them to be located quickly if they have wandered beyond the confines of the home. These devices are available from several providers.

The burdens of caregiving for someone with Down syndrome who has Alzheimer's disease can be significant. Therefore, it is also important to inquire about the welfare of the caregivers and provide acknowledgement, appreciation, and support.<sup>45</sup> Helpful resources are available from Down's Syndrome Scotland ([Living with Dementia](#)) and the National Down Syndrome Society ([Alzheimer's Disease & Down Syndrome: A Practical Guidebook for Caregivers](#)).

## Treatment of Associated Disorders

Adults who have DS-AD may develop other disorders that affect their well-being as well as complicate their treatment. These disorders are discussed in the articles [Common Health Conditions in Adults with Down Syndrome](#) and [Mental Health: Diagnosis and Treatment of Adults with Down Syndrome](#). There are several specific considerations when treating mental illness and/or behavioral change in individuals with DS-AD.

If psychiatric medications are needed to address behavioral and mood disorders, starting with low doses and increasing slowly can

reduce side effects. Especially in individuals with DS-AD, low doses (even low enough to be considered sub-therapeutic when treating those without Down syndrome) may be effective, and avoiding higher doses may limit negative effects including sedation and further cognitive impairment.

Shared decision-making discussions with individuals and their families can help determine which medications will improve quality of life. DS-AD may be associated with hallucinatory behavior, paranoia, or psychoses. Often this is not really a problem for the individual or those around the individual, and no treatment is needed. However, if this is disturbing to the person or is a safety issue, atypical anti-psychotics are sometimes prescribed. However, these medications have a “black box warning” from the Food and Drug Administration (FDA) and are not approved for dementia-associated psychoses.<sup>46</sup> Additionally, these medications are associated with increased mortality—mostly related to cardiovascular or infectious events—when used in people with dementia. If atypical antipsychotics are considered, a careful discussion about the risks and possible benefits should be undertaken. Common side effects of these drugs include unsteadiness, sedation, confusion, and incontinence; small doses may minimize these effects. A newer atypical anti-psychotic medication, brexpiprazole (Rexulti), has an FDA-approved indication for “dementia-associated agitation in patients with Alzheimer’s disease”<sup>47</sup> but still has a black box

warning against using it for dementia-related psychosis, as noted above.

If the change in behavior manifests as extreme upset or belligerence, an anti-epileptic medication may be prescribed. Because many individuals with DS-AD develop seizures, these medications may treat both the seizures and the behavioral changes. Clinically, valproic acid (Depakote), carbamazepine (Tegretol) or lamotrigine (Lamictal) are effective in some individuals. Levetiracetam (Keppra) works well for seizures in many individuals with DS-AD, but can cause fluctuating mood, or even aggression. If these behavior changes occur while on levetiracetam, changing to a different anti-epileptic medication may be beneficial. However, an assessment of other causes for the behavioral change (as noted above) may still be warranted.

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