Down Syndrome and Dementia

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This article reviews the advances in the evaluation and management of dementia in persons with Down syndrome. It is not inevitable that all older persons with Down syndrome will develop dementia. One of the major changes has been in the evaluation of dementia-like syndrome. This article will review laboratory tests as well as dementia scales, neuropsychological batteries and standardized mental status evaluations. Pharmacological management is also discussed. Lastly, there is a need for expert consensus on clinical guidelines for the evaluation and management of dementia in persons with Down syndrome.

Keywords: Alzheimer's disease, anticholinesterase inhibitors, dementia, dementia scales, Down syndrome

Clinicians and researchers have recognized the increased incidence of dementia in persons with Down syndrome for many years. Over one hundred twenty-five years ago, Fraser and Mitchell described a functional deterioration in persons with Down syndrome. In 1989, Lai and Williams estimated that between 55-75% of persons with Down syndrome 50 years and older would develop Alzheimer's disease. Furthermore, in a 1992 publication, Lai believed that if a person survived to their mid-fifties, the onset of clinical dementia of the Alzheimer-type was inevitable.

Studying a population-based sample of older persons with Down syndrome, Holland et al. calculated the prevalence of Alzheimer's disease for persons with Down syndrome aged 50-59 at 40%. Visser et al. studied 307 institutionalized persons with Down syndrome. Visser's group agreed with Lai that if persons with Down syndrome lived long enough, all would develop Alzheimer's disease. Visser et al. found that 17/22 (77%) persons with Down syndrome and aged 60-69 developed Alzheimer's disease. Note that Holland's somewhat more optimistic view was in a community sample, while Visser's studied an institutionalized population. As will be discussed later, an elderly woman with Down syndrome lived to her early 80's without evidence of Alzheimer's disease. Before discussing that dementia in older persons with Down syndrome is not inevitable, some terms should be clarified.

Dementia is the general term for conditions with multiple cognitive problems (not occurring only when the person has fluctuating consciousness). The main cognitive problems include disturbances of memory, planning, thinking, language, and motor behavior despite intact sensation. These cognitive problems should significantly impair overall functioning. There are several types of dementia, including two that have been described in persons with Down syndrome. The more familiar is Alzheimer's disease. The other is vascular dementia. Collacott et al. described a 55-year-old woman with Down syndrome and vascular dementia. Although Collacott's group believes that this form of dementia is underdiagnosed in Down syndrome, this is the only article about vascular dementia in Down syndrome. The remainder of this article will focus on Alzheimer's disease.

As noted above, most clinicians accept that Alzheimer's disease is not inevitable in older persons with Down syndrome. Case reports document older individuals with Down syndrome who do not develop dementia. Ms. K is a wonderful example. Ms. K had physical signs of Down syndrome including short stature, upward slant of her eyes, Brushfield spots, flattened occiput, short, curved fifth fingers, and prominent space between the first and second toes. When she died at the age of 83 from complications of a fractured hip, she had no clinical signs of dementia. It is important to approach the referral of a person with Down syndrome and possible dementia from differential diagnosis of possible reversible causes. (Table 1) Pary reviewed reversible causes of dementia. This article will not repeat the discussion of the potentially reversible conditions to be considered, but will highlight modifications of the dementia evaluation provided in the 1992 article.
**TABLE 1. DIFFERENTIAL DIAGNOSIS OF FUNCTIONAL DECLINE IN PERSONS WITH DOWN SYNDROME**

<table>
<thead>
<tr>
<th>Disorders Which are Common in Down Syndrome</th>
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<tr>
<td>- depression</td>
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<td>- hypothyroidism</td>
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<td>- Vitamin B12 deficiency</td>
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<tr>
<td>- sensory impairment (visual or hearing decline)</td>
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<tr>
<td>- chronic infection</td>
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<td>- malignancy (e.g., leukemia)</td>
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<td>- sleep apnea</td>
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<td>- orthopedic conditions resulting in chronic pain and decreased mobility</td>
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<tr>
<td>- other conditions (no apparent predilection for persons with Down syndrome)</td>
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<tr>
<td>(e.g., subdural hematoma, brain tumors, normal pressure hydrocephalus)</td>
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Adapted with permission, Pary

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**CLINICAL EVALUATION OF DEMENTIA IN PERSONS WITH DOWN SYNDROME**

Often, the first step in diagnosis is for the individual, family, or caregiver to recognize that there may be a problem. It is important for caregivers to be aware of normal aging in persons with Down syndrome. Indicators of the possibility of dementia include declines in bathing (now requiring prompts), dressing (no longer wearing clothes appropriate for the weather), and eating (no longer using forks or spoons correctly). Other indicators of possible dementia include getting lost in familiar places (in the neighborhood or in the home), losing occupational or social skills or showing significant personality changes.

The second step is for the clinician to consider the possibility of dementia as he or she hears about the person's problems in functioning. In 1996, the American Association on Mental Retardation (AAMR)/ International Association for the Scientific Study of Intellectual Disability (IASSID) developed practice for the clinical assessment of Alzheimer's disease in persons with developmental disabilities. These guidelines emphasize that some behavioral changes in persons with developmental disabilities may resemble Alzheimer's disease, but are caused by conditions that may be reversible.

Ironically, clinicians may be too focused on dementia. Smith believes that Alzheimer's disease may be overdiagnosed in people with Down syndrome because other causes of functional decline are overlooked. Cooper and Prasher caution that dementia is more than a decline in adaptive behavior. Prasher and Chung note that changes in adaptive skills may diagnostically point towards dementia, once sensory impairments, depression, and medical illnesses (e.g., hypothyroidism) have been ruled out. Nevertheless, declines in adaptive skills could also be merely age-related (and not dementia) because older people generally have more problems that can affect daily living skills (arthritis, decreased vision, etc.).

The third step is the decision by the clinician on whether to do the evaluation or refer to a tertiary center. The AAMR/IASSID guidelines note that the diagnostic evaluation can be conducted at several different kinds of places including university programs for intellectual (i.e., developmental) disability, geriatric assessment centers, memory disorder clinics, Alzheimer's disease centers, geriatric health care teams, general practitioners, geriatric psychiatrists, or neurologists. Ideally, the center should have experience evaluating older persons with Down syndrome. Unfortunately, there is no “gold standard tool” to diagnose Alzheimer’s disease in persons with Down syndrome.

**HISTORY AND PHYSICAL EXAM**

The most important diagnostic tools in the evaluation of Alzheimer's disease, whether it occurs in the general population or in persons with Down syndrome, remains the history from the caregiver and the observation/exam of the individual.
TABLE 2. RECOMMENDED LABORATORY TESTS FOR EVALUATION OF ALZHEIMER’S DISEASE IN PERSONS WITH DOWN SYNDROME

- Complete Blood Count
- Electrolytes
- Calcium
- Glucose
- BUN and Creatinine
- Liver Function
- Thyroid Function
- Serum B12
- Brain Imaging Computer Tomograph (CT) or Magnetic Resonance Imaging (MRI)
- Serology (syphilis)

Adapted from Beck et al. and Knopman et al.

Case Example

Mr. A is a 48-year-old man with Down syndrome and severe mental retardation. He was referred to the clinic for probable dementia. For the first fifty minutes the caregivers-informant provided graphs and descriptions of the functional decline. It was not until the evaluation was almost completed that the informant mentioned on direct questioning that the home was notified that Mr. A’s mother died nearly a year ago. Although his mother lived in the vicinity of the group home, no one notified the group home of the funeral. The group home staff did not find out until several months later when notified by a government agency. Although Mr. A was nonverbal, when asked about his mother, he looked noticeably sad. Mr. A’s functioning significantly improved after doing grief work including trips to his mother’s grave.

Laboratory Assessment

Over a decade ago, Pary reviewed the clinical evaluation of functional decline in persons with Down syndrome. Although laboratory tests were recommended, these tests were to diagnose other causes of functional decline (e.g., hypothyroidism). No laboratory test was recommended to aide in the diagnosis of Alzheimer’s disease. As health care has become more cost-conscious, it is no longer practical to order a comprehensive set of labs unless there is adequate justification.

Beck et al. reviewed 14 guidelines and consensus statements pertaining to the diagnosis of dementia and used nine to assess the most recommended diagnostic tests. Several tests mentioned in the 1992 article by Pary remain as part of the 2001 most recommended laboratory tests. (Table 2) These tests include complete blood count, thyroid function, electrolytes serum B12 and several tests on screening blood chemistries (calcium, liver function, blood urea nitrogen (BUN), creatinine, and glucose.

The only test recommended by Beck et al. and not routinely noted by Pary as part of a dementia work-up in persons with Down syndrome is serologic test for syphilis. It is debatable whether testing for syphilis should be part of the routine lab work-up in persons with Down syndrome and suspected Alzheimer’s disease.

The 1992 Pary article recommended several tests that now fall into the least recommended group as determined by Beck et al. (Table 3) Of the least recommended tests, brain imaging merits discussion. Beck et al. reviewed guidelines from nine groups. Seven groups did not recommend routine brain imaging. Only the AAN recommended computer tomography (CT) or magnetic resonance imaging (MRI). The Swedish Geriatrics Society recommended a routine CT. The main purpose of a CT or MRI is to detect several potentially reversible conditions.

Most of these conditions, however, would probably show lateralizing findings on a neurologic exam (and thus provide rationale for
TABLE 3. LABORATORY TESTS NOTED IN PARRY’S 1992 WORK-UP OF FUNCTIONAL DECLINE WHICH ARE LEAST RECOMMENDED TESTS

<table>
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<tr>
<th>Test</th>
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<tr>
<td>- Folate</td>
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<tr>
<td>- Urinalysis</td>
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<tr>
<td>- Electrocardiogram</td>
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<tr>
<td>- Chest X-ray</td>
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<tr>
<td>- Brain Imaging - Computer Tomography (CT) or Magnetic Resonance Imaging (MRI)*</td>
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Adapted from Beck et al.2
*AAN, Knopman et al.23 recommends structural neuroimaging with non-contrast CT or MRI as a guideline (most recommended)

Normal pressure hydrocephalus is a potentially surgically-responsive condition that could be diagnosed on CT or MRI. Other potentially reversible conditions detectable on CT or MRI include brain neoplasms, brain abscesses, or subdural hematomas. Both Beck et al. and the AAN23 agree that volumetric (quantitative) CT or MRI studies of hippocampal or entorhinal volume are not recommended at this time, although the hippocampus atrophies in Alzheimer's disease.

In the early nineties, there were no lab tests to diagnose Alzheimer's disease. Now there are several tests under investigation. The ideal diagnostic test for Alzheimer's disease should reflect the pathophysiology of the disease and be an early marker.3 The hallmarks of the neuropathologic changes in Alzheimer's disease are neurofibrillary tangles, senile plaques and neuronal loss. Tau is a protein released from neurons into the cerebrospinal fluid (CSF) as neurofibrils degenerate and form tangles. Amyloid is found in plaques. AD7C-NTP (neuritic thread protein) is associated with neuritic sprouting. Tau and beta-amyloid(1-42) are detectable in the CSF. They are touted as improving the diagnosis of AD.19 AD7C-NTP also has been studied in CSF of individuals with Alzheimer's disease.21 At this time, however, CSF tests for tau, beta-amyloid(1-42), or AD7C-NTP are not recommended in the routine clinical evaluation of Alzheimer's disease.2

Dementia Scales, Neuropsychological Batteries and Standardized Mental Status Evaluations

Scales have been designed to assist in the diagnosis of Alzheimer’s disease in persons with Down syndrome. These include the Dementia Questionnaire for Persons with Mental Retardation (DMR),12 and the Dementia Scale for Down Syndrome (DSDS).14 Deb and Braganza16 compared the DMR, DSDS and the Mini-Mental State Exam (MMSE). They found the observer-rated scales (e.g., DMR and DSDS) to be more clinically useful compared to the MMSE in persons with Down syndrome.

Another dementia scale in use is the Early Signs of Dementia Checklist (ESDC).33 The ESDC was used in a prospective study of Alzheimer's disease in institutionalized persons with Down syndrome. No study has compared the DMR, DSDS, and ESDC.

Neuropsychological testing is very challenging to perform as intellectual functioning becomes more severe. Several researchers have explored neuropsychological testing for Alzheimer’s disease in persons with Down syndrome.5,9,32 Generally, these tests have focused on cognitive issues (e.g., memory). Another neuropsychological approach measures personality and emotional functioning, the Neuropsychology Behavior and Affect Profile (NBAP).30 Similar to the dementia scales noted above, the test is designed to be completed by caregivers about the individual. At this time, neuropsychological batteries for persons with Down syndrome are still research tools confined to specialized centers.

Devenny11 developed a standardized approach to the mental status exam called the Institute for Basic Research Mental Status Exam. This exam is based on questions used in Alzheimer’s disease protocols in the general population. The exam tests orientation, memory, naming objects, rote memory, and fine motor skills.

Psychiatric rating scales used in studies of persons with Down syndrome and Alzheimer’s disease include the Present Psychiatric State for Adults with Learning Disability (PPS-LD). The scale covers psychiatric symptoms and...
maladaptive behaviors to generate psychiatric diagnoses.\textsuperscript{7}

In summary, there are a few rating scales, neuropsychological tests, semi-structured psychiatric evaluations to aid in the evaluation of Alzheimer’s disease in persons with Down syndrome. Research groups tend to develop their own instruments. Although some instruments were reviewed in 1995, others have been developed or refined since then.\textsuperscript{1} It is perhaps unfair to lump dementia scales, neuropsychological batteries, and semi-structured psychiatric evaluations together, but there does not appear to be a “gold standard tool” at this time. Clinicians may be forced to try the various tools to determine which are appropriate for their training/resources and which tools, if any, appear to significantly aid in the diagnosis.

**Management of Dementia in Persons With Down Syndrome**

The AAMR/IASSID practice guidelines offer practical suggestions for nonspecific medical management and supportive care.\textsuperscript{20} The care management guidelines are divided into early-, middle-, and late-stage practices. This approach is extremely practical and should help caregivers and clinicians develop relevant treatment and care plans. The AAMR/IASSID did not make any specific medication recommendations other than to practice good psychopharmacologic principles (e.g., fewest drugs at the lowest effective dose). If one looks to the developmental disability literature, specific pharmacologic treatment recommendations for dementia are murky and a little background is needed.

The neurotransmitter, acetylcholine, is deficient in Alzheimer’s disease. Although other strategies are being actively pursued, the main pharmacologic treatment designed to slow the progression of Alzheimer’s disease (but does not cure) targets acetylcholine; these drugs are called acetylcholinesterase inhibitors. They act on whatever acetylcholine that still remains in the brain synapses to be metabolized more slowly. Anticholinesterase inhibitors include tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl). Persons with Down syndrome were generally excluded from clinical trials. Hemingway-Eltomey and Lerner described three persons with Down syndrome and probable Alzheimer’s disease (aged 57 years, 59 years and 65 years). All three were tried on donepezil and in all three the medication was stopped because of side effects. One person became aggressive and agitated two weeks after donepezil was increased from 5mg to 10mg/day. Following discontinuation of donepezil, the agitation and aggression decreased. The other two individuals with Down syndrome who were on donepezil both developed urinary incontinence. In both cases, the incontinence stopped when donepezil was discontinued. Behavioral disturbances had been previously described in persons taking donepezil for Alzheimer’s disease in the general population.\textsuperscript{34}

Kishnani et al.\textsuperscript{22} gave donepezil to four individuals with Down syndrome. One person was 64-years old and had a decline of functioning for over two years. Another individual aged 38, with a decline in recent and remote memory, orientation, as well as increases in ill temper and perseverative behaviors, was given a diagnosis of dementia. There was insufficient information provided to determine if a thorough search for reversible causes was conducted. Donepezil was also given to a 24-year-old and a 27-year-old without diagnoses of dementia. Improvements were noted in communication, expressive language, attention and mood stability. It is premature to assume that any clinical improvement from donepezil in the 24-year-old and 27-year-old was due to the individuals having preclinical dementia. Donepezil has shown some response for young people with attention-deficit hyperactivity disorder (ADHD).\textsuperscript{35} Furthermore, donepezil markedly improved 6/11 individuals with treatment-resistant mood disorder.\textsuperscript{4}

Geldmacher et al.\textsuperscript{15} took a different approach to the pharmacologic treatment of functional decline in adults with Down syndrome. They recognized that six individuals with Down syndrome aged 23-63 were referred because of functional decline. There were varying degrees of memory problems, aggression, social withdrawal and compulsive behaviors. All received a selective serotonin-reuptake inhibitor (SSRI). All of the persons showed at least transient improvement per reports by caregivers. In a 63-year-old woman with Down syndrome, the family insisted that fluoxetine (40mg/d) be discontinued because of increased confusion.
myoclonus and insomnia. For a brief period, including following the cessation of fluoxetine, her crying spells improved and obsessive and agitated behaviors also improved. A year after the fluoxetine trial, she continued her behavioral and cognitive decline and required nursing home care; three years later she required total care.

SUMMARY

The past decade has seen a refinement of the initial laboratory work-up of dementia. There has also been more attention to different scales, semi-structured exams, etc. for the evaluation of possible dementia in persons with Down syndrome. There is a need for expert consensus clinical guidelines to examine the evaluation and treatment of dementia in persons with Down syndrome.

REFERENCES


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