Screening for Alzheimer’s Disease in Downs Syndrome

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Introduction

Downs syndrome (DS) is the most common genetic disorder seen in clinical practice and is associated with an increased incidence of dementia, notably Alzheimer’s disease (AD). Onset is earlier than in the general population [1] and recent advances in healthcare, which have seen average life expectancy for people with DS rise close to 60 years, [2] have increased its prevalence. In the context of the four life-stages described in DS, the last (> 40 years of age), senescence [3], is the typical stage of onset of AD.

The diagnosis of dementia in individuals with DS is difficult and is complicated by baseline intellectual disability (ID) [4]. No guidelines, within the DSM 4 or ICD 10 classifications, currently exist for diagnosing dementia associated with DS or any other learning disability. Thus, depending on the criteria employed and the population studied, prevalence of AD varies from 7% [5] to as high as 55% after 60 [6] and 75% by 65 years [7]. The unadjusted average prevalence rate of AD in DS is approximately 15% [8]. Prevalence rates for AD associated with DS also vary depending upon age [9] and baseline cognition [10]. Histopathogical studies have confirmed that hallmark changes consistent with AD are present in DS as young as the second decade of life and are found in 100% of cases by 60 years of age [11]. Despite this, just over half have clinical evidence of dementia and many living beyond 70, will never develop clinical AD [12]. Poor screening may account for underestimating the true prevalence [6].

Efficient and effective screening for AD in DS is required to diagnose, manage and exclude reversible causes. Although no specific guidelines exist, a clinical diagnosis is likely in the presence of new and progressive memory loss associated with deterioration across cognitive domains and activities of daily living (ADLs). Management of dementia including AD is similar to the general population, requiring prompt initiation to maximize benefit and is predominantly supportive. Although there is little strong evidence that pharmaceutical therapies, including cholinesterase inhibitors [13] and memantine [14], benefit those with DS patients with AD, treatment is often delayed, arguably reducing the therapeutic window [15]. Their use, as in the general population, requires knowledge of the disease stage. Older adults with DS often have significant co-morbidities [3] and it is important to also manage these. Although the prevalence of atherosclerotic complications, including cerebrovascular disease and vascular dementia, is low [7,16], older adults with DS have a relatively high prevalence of heart disease [17], obesity [18] and diabetes [19] for their age. Conditions mimicking dementia, such as thyroid disease, are also prevalent in DS and are frequently under-diagnosed. The lifetime prevalence of thyroid disease approaches 30% [20] and hypothyroidism in particular, is under-diagnosed. Depression, which can also mimic dementia, is common in DS [21] and should be screened for and treated.

Presentation of Dementia in DS

The predominant cognitive deficits in DS are in verbal short-term memory, explicit long-term memory and morphosyntax. Visuospatial, short-term memory, associative learning, and implicit long-term memory functions are usually preserved [7]. As with nondemented older adults, normal age associated cognitive changes are common in ageing adults with DS. Over the age of 40, the rate of decline, on neuropsychological testing, approaches 11% per year [22]. A selective pattern of cognitive changes is usually seen, characterized by impairment in long-term memory and visuospatial construction with relative preservation of immediate memory (recall) and language [23]. When dementia develops in adults with DS, it is characterized by global neuropsychological deficits, albeit with retention of some basic language skills [23], and often presents atypically [17]. Unlike the majority of cases of AD, people with DS developing AD, often present with frontal symptoms rather than with short-term memory loss [24]. This means that behavioural symptoms predominate [17], making it more challenging to separate AD from new onset behavioural disorders, or other psychiatric conditions such as depression, which are common in older adults with DS [25]. Deterioration in those with AD is associated with both age [26] and baseline cognitive ability [10]. Other atypical presentations include seizures and myoclonus, which are often a surrogate marker for the onset of dementia [27].

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General Principles of Cognitive Screening in Persons with DS

There is a need for coordinated healthcare screening, tailored to individuals with learning impairment [28] including DS. Dementia screening projects for people with DS highlight the lack of screening for dementia and other conditions [29]. Studies suggest a need to develop longitudinal rather than isolated, opportunistic screening approaches so baseline skills and abilities can be mapped and objective changes demonstrated to identify new cognitive impairments and evolving dementia. Some have suggested establishing this baseline by the age of 35 with annual reassessments [30], others that assessment should start at 25 with reevaluation at least every five years [4]. When change is established, a diagnosis is sought and appropriate person-centred care is provided to both client and caregiver alike [30]. As the presentation of dementia in DS is often atypical [17], when screening for dementia, it is important to consider changes in not only cognition but also personality, behaviour and ADLs. Sensory impairments such as hearing and visual problems are common [31] and may affect the ability to participate in cognitive testing. Screening is important as it allows prompt and appropriate initiation of care and treatment. Prompt assessment allows for the identification and exclusion of reversible causes.

Screening Tools in DS

Screening tools, specifically designed for detecting onset of dementia in persons with DS differ from screening tools for dementia in individuals without ID. In particular, they do not rely on cut-off scores but instead are based on combined functional and cognitive testing, ideally measuring change by comparing baseline with current status. Traditional screening instruments for detecting dementia, (like the Mini-Mental Status Exam (MMSE) [32] and its standardized form, the SMMSE [33]), or mild cognitive impairment (like the Montreal Cognitive Assessment [34] or Quick Mild Cognitive Impairment screen [35,36] were designed for people with average baseline intelligence and are of limited use in older adults with DS. These tests require developed language skills and attention, which can be impaired in individuals with ID [7]. The commonly used MMSE performs poorly when compared with observer-rated scales and could only be completed in 55% of test subjects with DS [37]. Other screening instruments that require compliance, dexterity, attention and language skills have not been validated in those with DS.

Clinicians require reliable and valid screening instruments that are responsive to change, measure a wide range of cognitive domains, identify changes early (high ceiling) and throughout the later stages of dementia (low floor). Although several screening tests for use in DS have been described, the agreement between different screening tests is reasonable and is generally in the order of between 70-75% [37]. Floor effects (high floor) are seen to a variable degree with most instruments developed or adapted for assessing cognition in DS. Screening or diagnostic tools suitable for screening for dementia in DS, can be either directly administered neuropsychological tests, or informant based observer-rated scales. When different instruments were compared, the observer-rated scales were superior to direct testing in assisting in the diagnosis of dementia in people with intellectual disability [37]. Individual screening instruments may not produce the most accurate results when screening for cognitive impairment in DS and have compared poorly to clinical judgment, which alone was found to be superior to a range of different tests [38]. Combined assessment using observer-rated questionnaires and direct neuropsychological testing may provide the highest sensitivity and specificity [37].

Observer-rated Scales

As many neuropsychological tests are not suitable or have not been validated for use in persons with developmental ages less than five or six [39], a collateral history is crucial to a diagnosis of dementia in persons with any ID, including DS. Given this, observer-rated scales, also called informant guided questionnaires or interviews, are often preferred over direct neuropsychological testing. Observer-rated scales must however, be interpreted with caution as ageing caregivers may be developing cognitive difficulties themselves or may know the subject too well or insufficiently to be objective [8]. Multiple informants should be consulted when subjects reside in institutional care [40]. While they include cognitive domains, they do not directly test cognition [27]. Several observer-rated scales have been developed, each with their own strengths and weaknesses (Tables 1 and 2).

Dementia Scale for Down Syndrome

The Dementia Scale for Down Syndrome [41] (DSQIID) is a useful
Down Syndrome

Gedye  
National Institute of Ageing  
Prasher et al.  
Hon et al.  
94%  
Roth et al.  
NA  
Haxby  
Cognition  
Evenhuis  
Albert and Cohen  
Table 1: Comparison of the advantages and disadvantages of different assessment instruments for dementia in persons with Downs syndrome.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Instrument</th>
<th>Cognition assessed</th>
<th>Behaviour assessed</th>
<th>ADLs assessed</th>
<th>General Disability assessment/ global assessment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer rated scales</td>
<td>DSDS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Gedye [41]</td>
</tr>
<tr>
<td></td>
<td>DMR</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Evenhuis [42]</td>
</tr>
<tr>
<td></td>
<td>CAMDEX-DS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Roth et al. [43]</td>
</tr>
<tr>
<td></td>
<td>DSQIID</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Deb et al. [31]</td>
</tr>
<tr>
<td>Neuropsychological tests</td>
<td>DSME</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Haxby [23]</td>
</tr>
<tr>
<td></td>
<td>CAMCOG-DS</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Hon et al. [45]</td>
</tr>
<tr>
<td></td>
<td>TSI</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Albert and Cohen [47]</td>
</tr>
<tr>
<td>Adaptive behaviour tests</td>
<td>ABDQ</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Prasher et al. [51]</td>
</tr>
<tr>
<td></td>
<td>DLSQ</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>National Institute of Ageing [53]</td>
</tr>
</tbody>
</table>

+ Domain included  
- Domain not included

The Dementia Questionnaire for Mentally Retarded Persons (DMD) [42] is an English translation of a Dutch questionnaire, the Dementie Vragenlijst voor Zwakzinnigen (DVZ). It is based upon the observations of caregivers over the previous two months. The DMD has a specificity and sensitivity of 92% for the diagnosis of dementia in persons with ID, including DS, and compares favourably with the DSDS and MMSE [37]. The questionnaire has 50 items (8 subscales) divided into two subcategories: cognitive scores (short term memory, long-term memory, spatial and temporal orientation) and social scores assessing speech (including conversation), practical skills, mood, activities, interests and behaviours. The questionnaire provides three response categories, ranging from zero (no deficit) to two (severe deficit), with higher scores corresponding to greater severity. The DMD, unlike the DSDS, doesn't require specialised training, contains a useful measure of general disability and is also quick to use (15-20 minutes). It is poorly sensitive in advanced dementia due to floor effects, necessitating the use of cut-off scores adjusted to the level of ID. An abbreviated form is also available.

**The CAMDEX-DS**

A modified version of the informant interview of the Cambridge Examination for Mental Disorders of the Elderly [43], the CAMDEX-DS [44] can be used to document increasing prevalence with age [9]. The CAMDEX-DS, designed for use in the community, by trained
healthcare professionals, consists of both an informant interview and participant neuropsychological assessment. It assesses memory, general intellectual function, judgment, general performance, higher cortical function and personality. The CAMDEX-DS has good interrater reliability and predictive validity [44], when conducted with an informant who knows the subject for at least six months. The authors caution that it is a diagnostic aid rather than a screening tool. A floor effect is also demonstrated with the CAMDEX-DS.

Dementia Screening Questionnaire for Individuals with Intellectual Disabilities

The Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQID) [31] was derived from interviews with caregivers of 24 adults, aged between 48 and 72, with DS and dementia. It has 53 items, divided into three parts and has excellent internal consistency, test-retest reliability and interrater-reliability. The first part assesses baseline 'best' ability; the second part scores behaviours and symptoms suggestive of dementia (43 questions, scored on a four point scale with "always has been the case" and "does not apply" scoring zero points and "always but worse" and "new symptoms" scoring one). The third part provides ten comparative questions answered yes (one point) or no (zero points). Scores from part two and three are summed to provide a total score. A cut-off score of 20 provides optimal sensitivity and specificity, 92% and 97% respectively. The DSQID was validated in a large sample of DS subjects with dementia, larger than either the DSDS or DMR. The DSQID is quick (10-15 minutes) and is easy to score in any setting. The single, fixed cut-off, may limit its usefulness in more advanced stages of dementia and in individuals with varying degrees of baseline ID.

Neuropsychological Tests

The DSMSE

The Down Syndrome Mental Status Examination (DSMSE) [23], comprises several cognitive domains including: orientation (days of the week, seasons), personal information, short-term memory, language (confrontation naming of clothing and body parts), visuospatial construction and praxis. It has a strong emphasis on verbal skills. The test was validated in a small initial sample, demonstrates a floor effect and is less sensitive than other neuropsychological tests [27].

The CAMCOG-DS

The Cambridge Cognition Examination or CAMCOG, the self-contained neuropsychological component of the CAMDEX, has been validated in subjects with DS [24,45]. The CAMCOG-DS contains seven different subscales including orientation, language, memory, attention, praxis, abstraction and perception, which were either taken directly from the CAMCOG or modified from the Severe Impairment Battery [46]. The total score is 107 points. Although some tests of executive function were deemed too difficult and were removed, verbal fluency and ‘similarities’ remain as surrogate tests of executive function. The CAMCOG-DS has few floor effects and correlates with the age and MMSE scores [45].

The Test for Severe Impairment (TSI)

The Test for Severe Impairment or TSI [47], originally developed for use in the general adult population, has been validated in persons with ID [27]. The TSI consists of six subsections, including motor performance, language, immediate and delayed recall, conceptualization and general knowledge, each with four questions providing a total score of 24 points. Eight questions require the subject to respond verbally. Brief and easy to use without significant ‘floor’ or ‘ceiling’ effects [27], it provides a wider range of scores than tests such as the DSMSE [48]. It also has excellent reported internal consistency, interrater reliability and test-retest reliability [27].

The DAMES Score

The DAMES (Down’s syndrome attention, memory, and executive function scales) score [22] is a neuropsychological test, validated specifically in older adults with DS. Consisting of 11 domains, it has three summaries (attention, executive function, and memory), providing a total score of between 0 and 222. Higher scores indicate better cognition.

Excluding Depression

As with dementia screening for the general population, it is important to exclude co-morbid depression. Separating dementia from other psychiatric conditions, particularly depression is challenging. Depression is common in DS [25], frequently undertreated [21] and associated with dementia [49]. The highest prevalence is seen in those with mild to moderate ID [25]. Those with DS are vulnerable to depression and several risk factors have been proposed including small hippocampal volumes, changes in neurotransmitter systems, deficits in language and working memory, attachment behaviours and somatic disorders [21]. Depression in adults with DS usually presents as a decline in social discourse [50]. Few instruments have been validated, to differentiate between dementia and depression, in adults with DS.

Measures of Adaptive Behaviour

Decline in adaptive functioning beyond baseline levels is a diagnostic feature of dementia. Tests of adaptive behavior measure an individuals’ ability to function socially and perform ADLs. The Adaptive Behaviour Dementia Questionnaire (ABDQ) [51] is a 15-item questionnaire, derived from the Adaptive Behaviour Scale [52], and used to detect change in adaptive behavior in DS. The ABDQ is reliable and valid, demonstrating excellent accuracy (92%), in identifying dementia in older adults with DS. The Daily Living Skills Questionnaire (DLSQ) [53] is also of use in measuring ADLs [27,54]. Informants provide information concerning a variety of ADLs including dressing, grooming, eating, manual dexterity and geographical orientation.

Conclusion

Cognitive screening in persons with DS or other intellectual disabilities is challenging and presents several important obstacles. Baseline cognition limits both initial and interval assessments, making the diagnosis difficult. DS is also associated with a normal-age related cognitive decline and differentiating this from dementia is equally challenging. As AD often presents atypically in DS, with frontal type cognitive decline and differentiating this from dementia is equally challenging. As AD often presents atypically in DS, with frontal type behavioural disturbance and loss of function, onset can be overlooked or misattributed. The rules that normally govern cognitive screening, such as the use of age and education adjusted cut-off scores [55], are difficult to define and apply in DS. Floor effects, language skills, and assessment variability due to behavior and cooperation also limit tests [56]. The evidence base for treatment of AD in DS is as yet unclear, and can be attributed to insufficient or delayed treatment [15], highlighting the need for prompt screening and detection to ensure better outcomes. Finally, healthcare professionals may not feel that screening for AD is a priority or presume its inevitability in all older adults with DS. To overcome this, campaigns such as the United Kingdoms "It's your move: Down's syndrome and dementia" programme, were developed.
to increase awareness of screening issues, particularly in primary care. This is important, as cognitive screening should also be considered an appropriate time to initiate general health screening in all older adults with DS. Guidelines such as the Edinburgh Principles [57] provide a useful ethical framework to guide care of persons with DS and AD.

Further research is needed to determine if long-term screening programmes for AD or other forms of dementia in adults with DS will be clinically or cost-effective. At present, no rapid screening tool has been validated in this population and it is uncertain at which age screening will begin. It is likely that no single, one-dimensional screening tool will suffice. As with screening for dementia in the general population, identifying early dementia is most challenging [37]. Given that clinical judgment alone is currently superior to screening tests [38], it would seem that there is a need to combine detailed clinical assessment with informant history and standardized neuropsychological testing to improve diagnostic accuracy. Although a working battery of tests, like that proposed by the International Disability and the American Association on Mental Retardation [30] can be used, they are limited by time constraints. Instruments measuring functional level, scored in the context of suggestive clinical features like age and new onset epilepsy [27] may prove the most useful.

The course of AD in DS is not detached from the wider study of dementia. Understanding of its onset, progression and management in DS will also improve and further the management of AD in the general population [58]. Only if the diagnosis is made early, will it be possible to intervene and improve management, with both pharmacological and non-pharmacological therapies, to benefit both older adults with DS and caregivers alike.

References