Original

The usefulness of standard neuropsychological testing for adults with Down syndrome and dementia*

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Abstract

Background: Subjects with Down syndrome (DS) have an increased risk of Alzheimer's disease (AD). As intellectual ability is lower in DS subjects than among the general population, it is difficult to determine whether cognition has deteriorated with age to the point of fulfilling AD diagnostic criteria. The Mini-Mental State Examination (MMSE) and the Severe Impairment Battery (SIB) are standard cognitive tests widely used to assess dementia in the general population. There are few studies using the MMSE and the SIB on subjects with DS where dementia is suspected. The aim of the present study was to analyse the appropriateness of the SIB and the MMSE in the cognitive assessment of aging subjects with DS.

Methods: The SIB and the MMSE were administered to 45 subjects with DS (16 with Alzheimer's disease and 29 without dementia), and the DMR questionnaire was given to their caregivers.

Results: DS subjects with dementia had higher impairment levels than DS subjects without dementia in their social and total DMR scores, but no significant differences were found between the two groups in the SIB and MMSE scores or in cognitive DMR performance. Overall, SIB scores correlated significantly with MMSE results, total DMR, cognitive DMR, and social DMR. MMSE performance correlated significantly with total and cognitive DMR scores as well as SIB score.

Conclusion: The SIB and the MMSE are useful assessment tools in monitoring cognitive function among subjects with DS and cognitive loss or dementia.

Keywords: Dementia. Cognition. Alzheimer's disease. Down syndrome.

Introduction

Down syndrome is the most widespread and easily identified condition linked to mental retardation. It is caused by a genetic disorder involving the presence of three copies of chromosome 21 (trisomy 21) instead of the usual two. The additional copy of the chromosome leads to altered development of the brain and other parts of the body. Mental retardation and certain specific physical traits are therefore characteristic of DS. In most cases, diagnosis is arrived at by a genetic (karyotyping) test performed shortly after birth.

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The diagnostic definition of mental retardation developed in 1992 by the American Association on Mental Retardation comprised low intellectual quotient (IQ) and adaptive shortcomings. Currently, the prevailing conceptual approach to intellectual disability is a bio-psycho-social model emphasizing the idea of disability as the outcome of the interaction between individuals and their environment. According to the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision), the diagnostic criteria for mental retardation are as follows: a) significantly subaverage mental functioning (an IQ of 70 or less in an individually administered intelligence test); b)concurrent deficits or impairments in present adaptive functioning (i.e., the person's effectiveness in meeting the standards expected for his or her age by his or her cultural group) in at least two of the following areas: communication, self-care, home living, leisure, social/interpersonal skills, work, use of community resources, health, and safety; c) onset before age 18 years (1).

Individuals with DS tend to age prematurely and develop neuropathological patterns typical of Alzheimer's disease (AD), such as amyloid deposits and neurofibrillary tangles, at a relatively early age, often with no clinical signs or symptoms of AD. Some of these individuals progress to clinical dementia; the rate increases with age. Subjects with DS are at an elevated risk of developing dementia after the age of 30 (2,3,4). Signs and symptoms of dementia are found in 25% of those older than 35-40 years, with variability rising to a range of 30% to 75% of those in the sixth decade of life (5). Mean age of onset of dementia in patients with DS is 50 years (6,7). However, there have been case reports of patients who reached their 80th birthday without meeting diagnostic criteria for dementia (8).

It is a well-known fact that AD gradually impairs a subject's cognitive abilities, including attentional functions, memory, language, praxis, perception, and the executive and visuospatial functions. Hence, there is a gradual deterioration in the subject's performance of everyday life activities (9,10,11).

The link between AD and chromosome 21 has been corroborated by a number of clinical and experimental findings based on epidemiological genetic approaches and molecular biology (7,12). At least one familial type of AD has been linked to a genetic defect in chromosome 21 (13,14). Pathological and clinical signs of AD develop prematurely in subjects with DS (trisomy 21), and it is believed that overexpression of one or several genes in chromosome 21 (such as APP, the gene for amyloid precursor protein) can give rise to an AD phenotype (15,16,17). The APP6 allele has been linked to age of onset of dementia in individuals with DS (7).

With baseline intellectual level in DS lower than the general population average, it can sometimes be hard to gauge objectively whether a patient's abilities and skills are becoming impaired with age to an extent that fulfills AD diagnostic criteria. Diagnosing dementia in patients with intellectual disabilities, particularly in the early stages, can therefore be quite challenging (18). Moreover, it is important to rule out other non-AD causes of dementia, such as cerebrovascular lesions, thyroid disorders, depression disorder, brain tumors, brain clots, metabolic disorders, and so forth.

Although the criteria used to confirm deterioration are not absolute, evidence of gradual loss of function other than the normal effects of aging is a requirement (19). Deterioration may be noted for memory and other cognitive functions, orientation, emotional control, motivation, and social behavior (20).

According to CDR-10 (Clinical Dementia Rating) diagnostic criteria, a diagnosis of dementia in subjects with DS requires significant declines in cognition, mental state, behavior, and social functioning (19). Metrics that are sensitive to cognitive change are therefore essential.

There are specific scales that use information reported by caregivers and family members to assess cognitive functioning and behavioral symptoms of patients with DS to test for dementia. One such scale is the Dementia Questionnaire for Mentally Retarded Persons (DMR), designed as a screening test (21, 22, 23) and comprising 50 items that provide a sum of cognitive scores (SCS) (for short- and long-term memory and temporal and spatial orientation) as well as a sum of social scores (SOS) (for language, practical skills, mental state, activities and hobbies, and altered behavior). The subjective views of the informant thus bias and impair objectivity in the cognitive assessment of adults with DS.

Some neuropsychological tests originally developed to diagnose dementia for the mainstream population have been modified for patients with intellectual disabilities (18), chief among them the Mini-Mental State Examination (MMSE) (24). This test was used in an EEG study to screen out subjects with DS who did not fulfill the criteria for dementia (25). However, some

authors have suggested that the MMSE does not appear to be a useful tool because subjects with DS without dementia score less than 24, the diagnostic cut-off point for the general population. A «floor effect» has even been identified (18, 26).

However, patients with severe dementia are usually rated using the Severe Impairment Battery (SIB), which has been validated for these patients and is used to evaluate the lower ranges of cognitive performance (28). Witts and Elders (29) pioneered the assessment of the SIB's effectiveness in evaluating cognition on 33 adults with DS. They found the test to be highly reliable in terms of its correlation with the subjective Vineland Adaptive Behavior Scale (VABS). The SIB has also been used to assess the effectiveness of donepezil treatment in patients with DS and AD (30).

Another objective cognitive test for dementia in subjects with DS is a modified version of the Selective Reminding Test, which pinpoints declarative memory disturbances in the early stages of DS (31).

The present study considers the utility of routinely used standardized tests for dementia to assess cognitive function in adults with DS, with a specific focus on the MMSE and SIB.

Method

Subjects

The population sample assessed in the present study was enrolled in a previously published trial of donepezil involving 99 adult subjects with DS (32). Out of a total of 99 subjects older than 40, 45 displayed cognitive impairment objectively confirmed using the Early Signs of Dementia Checklist (ESDC) (33). The 45 subjects who displayed signs of cognitive deterioration and/or disturbed behavior were evaluated and clinically examined for differential diagnosis, and rated as having probable AD, potential AD, or absence of AD criteria. Karyotyping was used to confirm trisomy 21 in all subjects.

Enrollment criteria were karyotype-confirmed DS, age over 40 years, and either gender. Exclusion criteria were depression; hypothyroidism; vitamin B_{12} and/or folic acid deficiency; a positive serum test for lues; an active or unstabilized heart condition; the researcher's judgment that a prior condition linked to cognitive deterioration might interfere with diagnosis of AD; altered consciousness (delusions); sleep apnea; radiologically confirmed atlantoaxoid dislocation; drug-originated cognitive impairment; known intolerance to donepezil; and lack of written consent by the patient or their legal representative.

The present study analyzed a total of 45 subjects (23 male, 22 female) with a mean age of 47.4 years (±5,39, range 39-62). Three of the patients (6.6%) had mild mental retardation, 39 (86.8%) had moderate mental retardation and the remaining 3 (6.6%) had severe mental retardation. Differential diagnosis was based on neurological examination, history-taking and the DMR scale, and the final result was that 29 subjects did not have dementia, 5 had potential dementia and 11 met the criteria for probable dementia (9).

Clinical assessment

Two objective cognitive tests were administered to all patients: the SIB (34) and MMSE (24). Additionally, the subjective DMR test (35) was administered to caregivers.

The Severe Impairment Battery (SIB) (36) can evaluate the lower range of cognitive abilities. It includes subtests for orientation, attention, memory, language, visuospatial ability, praxis, and social interaction, with total score ranging from 0 to 100 (from minimum to maximum performance).

The Mini-Mental State Examination (MMSE) (24) is the screening test most widely used to assess cognitive function in studies of patients with dementia. It consists of 30 items that consider orientation in time and space, attention/concentration, memory, verbal comprehension, praxis, and language. The maximum score is 30, and any score below 24 indicates cognitive deterioration in the general population (37,38).

The Dementia Questionnaire for Mentally Retarded Persons (DMR) comprises 50 items which produce two scores – the sum of cognitive scores (SCS) (for short- and long-term memory as well as visual and spatial orientation) and the sum of social scores (SOS) (for language, practical skills, mental state, activities and hobbies, and behavior).

Statistical analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS, Chicago, IL). Sample

descriptive data were calculated and t-tests were used to compare the MMSE, SIB and DMR (cognitive, social and total) scores of the two groups in the study (subjects with DS with or without dementia). Pearson's correlation coefficient was used to gauge correlation between the subjective scale routinely filled out by caregivers of the individuals with DS, DMR-SCS and the two objective cognitive tests (MMSE and SIB).

Results

Subjects who had DS and dementia had scores indicative of greater disturbance in the DMR total score and social score, compared to those without dementia. However, no significant differences were found between the scores achieved by subjects with or without dementia on the SIB, MMSE and cognitive DMR (Table I).

SIB scores significantly correlated with MMSE scores (r=0.768; p=0.0005), total DMR scores (r= -0.506; p=0.0005), cognitive DMR scores (r=0.522; p=0.0005) and social DMR scores (r= -0.383; p=0.009) (Figures 1 and 2). Moreover, the MMSE score correlated significantly with the total DMR score (r=-0.495; p=0.001) and cognitive DMR score (r=-0.507; p=0.0005).

Discussion

The present study found a statistically significant correlation between the two objective cognitive tests, MMSE and SIB, and the subjective DMR cognitive subscale. This finding suggests that the MMSE and the SIB may be of use to assess cognitive function in adults with DS. The results of subjects in the present study are consistent with the findings of Witts and Elders (29), who reported high validity and test-retest reliability of SIB, though only adults with DS but no dementia were assessed. The authors used the Vineland Behavior Functional Scale to validate the SIB.

However, our comparison of subjects with DS with dementia versus those without shows significant differences in DMR total and social scores, but merely a trend in the case of the cognitive DMR score. These findings are consistent with those of other authors who assert that the earliest symptoms of dementia in subjects with DS are best detected among non-cognitive functions, such as psychological symptoms or changes in social skills (18,33,39).

Our findings suggest that a functional scale (such as the DMR) is more appropriate to screen

Table I. Differences between SIB, MMSE and DMR scores of DS subjects with and without dementia

	No dementia mean (SD) (n=29)	With dementia mean (SD) (n=16)	*t* (43)	p
SIB	64,03 (22,33)	54,86 (24,77)	1,23	0,224
MMSE	8,74 (6,44)	6,57 (5,57)	1,09	0,282
DMR-total	24,19 (12,47)	45,00 (13,28)	-5,08	0,0005
Cognitive-DMR	15,68 (10,68)	22,50 (11,44)	-1,91	0,059
Social-DMR	11,68 (5,82)	17,50 (8,92)	-2,23	0,038

SD: standard deviation; SIB: Severe Impairment Battery; MMSE: Mini-Mental State Examination; DMR: Questionnaire for Mentally Retarded Persons.

Figure 1. SIB and MMSE scores.

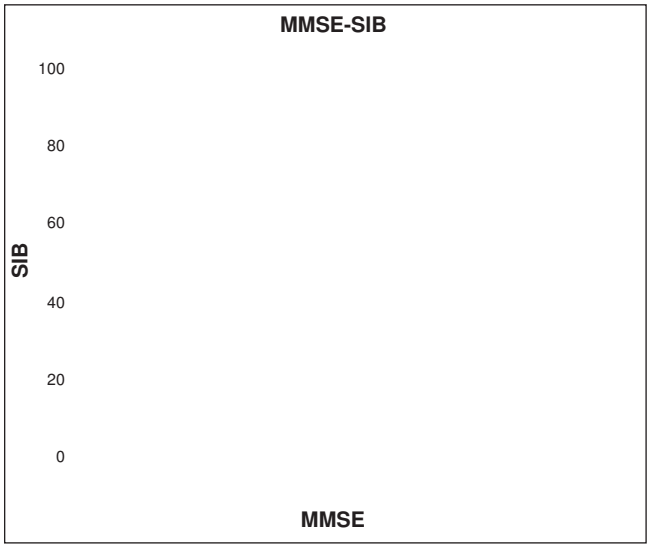
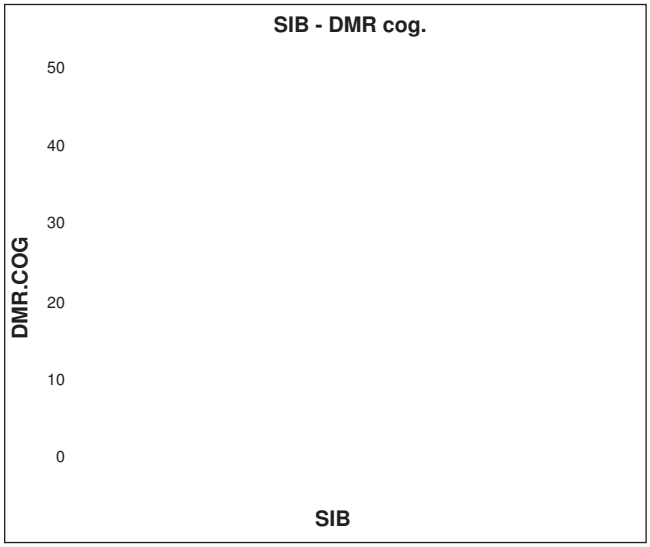


Figure 2. Dementia Questionnaire for Mentally Retarded Persons and SIB scores.



adults with DS for dementia. Still, from the clinical standpoint, the need to monitor cognitive function makes it advisable to use objective scales such as the MMSE and the SIB, as opposed to subjective scales such as the DMR-SCS or the Dementia Scale for Down Syndrome, which are completed using information reported by the patient's carer or guardian. Subjective scales may be highly disorder-specific, but lack sensitivity to change (40). Since SIB scores showed greater variability than MMSE scores, and given the fact that the SIB was designed to assess subjects with low MMSE scores, we would advise the use of the SIB as the most appropriate test battery for subjects with DS and cognitive deterioration (26).

In conclusion, while the SIB and MMSE may not be relevant to the diagnosis of Alzheimer dementia in subjects with DS, they may play a highly useful role when it comes to monitoring cognitive deterioration and dementia in these subjects. We therefore advocate their widespread routine use, so examination time can be reduced by applying these more objective methods, which also allow a comparison with mainstream populations.

Replication of the present study with a larger sample and yearly follow-up would help advance knowledge of Alzheimer dementia in people with Down syndrome.

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