

Down's syndrome and dementia

Lisa R. Stanton & Rikus H. Coetzee

Abstract Down's syndrome is the most common genetic disorder seen in clinical practice: about 94% occurs because of non-disjunction of chromosome 21 and 3–5% because of translocation. Individuals increasingly survive to middle and old age, probably because of advances in medical treatment and improved living conditions. People with Down's syndrome have an increased risk of developing Alzheimer's disease in middle age. Within ICD-10 and DSM-IV classifications there is no consensus on the diagnosis of dementia in people with learning disability. New treatments have been licensed for use in mild to moderate Alzheimer's disease (e.g. acetylcholinesterase inhibitors and memantine). The comorbid picture of Down's syndrome and Alzheimer's disease presents a unique challenge to the clinician in both diagnosis and management.

Epidemiology and aetiology

Prevalence at birth of Down's syndrome increases with maternal age, ranging from 0.7/1000 births for mothers aged 20–24 years to 55/1000 births for those aged 45–49 years. The IQ of people with Down's syndrome is usually in the mild to moderately severe range of the learning disability spectrum (IQ < 70). The prevalence of Alzheimer's disease in people with Down's syndrome rises with increasing age, and prevalence rates varying from 6% to 75% have been reported (Rabe *et al*, 1990; Visser *et al*, 1997). A recent study of 285 people with Down's syndrome found a 13% prevalence of Alzheimer's disease (Tyrell *et al*, 2001). Age-related cognitive decline and frontal lobe dementia appear to be more prevalent in the younger age groups (30–49 years of age), and frontal lobe dementia appears to be more prevalent in those with more severe learning disability, but this needs to be confirmed by further studies (Holland *et al*, 2000). It is possible that early-onset cases present with more frontal symptoms and this may represent a different clinical subtype of Alzheimer's disease in Down's syndrome. There appears to be no relationship between level of learning disability and risk of dementia or age at onset of dementia (Holland *et al*, 1998). The rate of deterioration appears to increase with age (Oliver *et al*, 1998). The level of pre-existing cognitive function is also closely associated with the rate of decline (Temple *et al*, 2001).

Neuropathology

Although senile plaques and neurofibrillary tangles may be widespread in the brains of people with Down's syndrome, not every affected individual develops Alzheimer's disease. Alzheimer's disease is associated with characteristic neuropathological changes in the brain, including the deposition of extracellular β -amyloid in neuritic plaques and the formation of intracellular neurofibrillary tangles. These cause the death of the neurons that contain them (Wisniewski *et al*, 1985). These tangles comprise neuronal inclusions of abnormal cytoskeletal components and abnormally phosphorylated tau protein. Increase in the number of plaques containing fibrillised β -amyloid is seen in people with Down's syndrome after the age of 50 years and is associated with neuronal loss. Presence of diffuse plaques, however, shows no such association with the onset of Alzheimer's disease (Schupf, 2002).

The formation of β -amyloid occurs through the splitting of amyloid precursor protein coded for by a gene on chromosome 21. The β -amyloid is cleaved to form the peptides AB1–40 and AB1–42. It is thought that an important stage in the development of Alzheimer's disease is deposition of AB1–42, and this is associated with cognitive decline. Abnormal karyotypes that decrease the amyloid precursor protein dose, for example translocations, are associated with a reduced risk of Alzheimer's disease.

Lisa Stanton is a specialist registrar in old age psychiatry and general adult psychiatry in Nottingham (Nottinghamshire Healthcare NHS Trust, Duncan Macmillan House, Porchester Road, Nottingham NG6 3AA, UK. E-mail: Liza.Stanton@nottshc.nhs.uk). Her research interests are in liaison in old age psychiatry, the interface between old age psychiatry and learning disability services, and neuropsychiatry. Rikus Coetzee is also a specialist registrar in general adult psychiatry and old age psychiatry at Duncan Macmillan House, Nottingham. His research interests are in the treatment and epidemiology of trauma-related neurosis in the elderly and the use of cognitive-behavioural therapy with elderly people.

The increased risk of dementia in people with Down's syndrome is thought to be associated with overexpression of the amyloid precursor protein gene. However, there is a wide variation in the age at onset of dementia in people with Down's syndrome and this does not appear to be solely attributable to overexpression of amyloid precursor protein. Mutations in the genes for amyloid precursor protein and presenilin 1 and 2 are associated with familial Alzheimer's disease, which is often of early onset.

It is thought that people with Down's syndrome who have Alzheimer's disease are similar to people with familial Alzheimer's disease, in that the onset of dementia is usually early. It should be noted that the mothers of individuals with Down's syndrome seem to have a specific vulnerability to developing Alzheimer's disease. A comprehensive review of the genetic aspects of the disease in Down's syndrome is given in Schupf *et al* (2001) and Schupf (2002).

The early age at which people with Down's syndrome develop Alzheimer's disease may be due to a variety of factors. Apolipoprotein E (ApoE) is a polymorphic lipoprotein found in the brain. In health, its role involves nerve sheath repair (Mann *et al*, 1996). There are three common variants of the gene for APOE (alleles APOE ϵ 2, APOE ϵ 3 and APOE ϵ 4). Numerous studies have shown that the presence of the ϵ 4 allele is associated with early onset of Alzheimer's disease, whereas the presence of the ϵ 2 allele is associated with a delay in disease onset and is possibly protective. The effects of the ϵ 3 allele appear to lie somewhere between those of the ϵ 4 and ϵ 2 alleles. In women before the menopause, oestrogen promotes the growth and prolongs survival of cholinergic neurons and has antioxidant properties. It also prevents formation of β -amyloid by regulating amyloid precursor protein metabolism. Menopause occurs earlier in women with Down's syndrome (Seltzer *et al*, 2001). It is thought that the loss of oestrogen may be important in the development of Alzheimer's disease in women, and women treated with hormone replacement therapy (HRT) seem to have a markedly reduced risk of developing the disease. However, HRT given to women with cognitive impairment does not appear to prevent further decline. It is unknown what the effect of HRT might be in men.

Clinical presentation

Potential difficulties in making a diagnosis

The clinical picture of Alzheimer's disease in Down's syndrome is complex, owing to the pre-existing cognitive impairment and atypical

presentation. Difficulties with making a psychiatric diagnosis in a person with Down's syndrome include 'psychosocial masking'. This refers to the unsophisticated social skills and lack of life experiences that a person with learning disability might exhibit, which can alter the presentation of symptoms. People with Down's syndrome may not present their symptoms verbally, because of their impaired communication skills. In fact, carers might be more likely to highlight a change than would the person with Down's syndrome.

'Diagnostic overshadowing' (Reiss *et al*, 1982) means the attribution of changes in behaviour or ability to learning disability. For people with Down's syndrome, diagnostic overshadowing can mean that they are referred to specialist services late or not at all. When learning disability is present, diagnostic overshadowing seems to reduce the significance attached to abnormal behaviour which might otherwise have been attributed to psychiatric disorder. In addition, some abnormal behaviours may be seen as less significant than the learning disability itself. Taken to its fullest extent, the behaviour may be attributed solely to the intellectual impairment, rather than to a psychiatric disorder such as dementia.

Another difficulty results from the exacerbation of cognitive deficits and maladaptive behaviours that pre-date the dementia. This is known as 'baseline exaggeration', and it can make determining the onset of dementia difficult in people with learning disabilities. Finally, intellectual distortion (reduced abstraction) and often the reduced ability to communicate clearly can lead to difficulty in identifying subjective symptoms.

Even if a dementia is diagnosed it should be remembered that changes in presentation might be due, or partially due, to social or emotional difficulties.

Presentation of dementia in Down's syndrome

Early-onset symptoms may vary from person to person, but there is evidence that the acquisition of deficits tends to mimic those seen in Alzheimer's disease generally (Oliver *et al*, 1998). Deterioration in memory, learning and orientation tend to be the first signs, and these symptoms are often accompanied by increased dependence (Cosgrave *et al*, 2000). Personality change is often associated with early involvement of the frontal lobes (Holland *et al*, 2000). It has also been reported that Alzheimer's disease in Down's syndrome presents with a greater prevalence of low mood, excessive overactivity/restlessness, disturbed sleep, excessive uncooperativeness and auditory hallucinations (Cooper &

Prasher, 1998). Delusions and hallucinations do occur in people with Down's syndrome and dementia, but they may be a less prominent feature than in dementia alone. The reasons for this, however, remain unclear.

It should be remembered that there is cognitive decline associated with ageing in Down's syndrome. Receptive and expressive language, short-term memory and non-verbal reasoning can be preserved, but there are known to be slight declines in verbal and long-term memory for those over 50 years of age and the ability to form long-term memories and visuospatial construction may become slightly impaired. For an individual who is developing dementia, however, there are significant deficits in learning and memory. It is important to correctly differentiate age-related cognitive decline from early dementia. It must, however, be kept in mind that for people with Down's syndrome over the age of 40, decline in functioning is not inevitable. Box 1 summarises the clinical symptoms of Alzheimer's disease in Down's syndrome.

Investigation and differential diagnosis

At present there is no generally accepted definition of Alzheimer's disease in people with learning disability, although the diagnostic criteria for psychiatric disorders for use with adults with learning disabilities (DC-LD; Royal College of Psychiatrists, 2001) include general criteria for the diagnosis of dementia in learning disability using an axis classification. The DC-LD also differentiates between Alzheimer's disease, vascular dementia and delirium, but not dementia with Lewy bodies. In addition, there must be no evidence for any other cause of dementia on history and investigation.

Consensus criteria for diagnosing dementia in people with Down's syndrome have been suggested by a working group set up to establish such criteria (Aylward *et al*, 1997). The group suggests that ICD-10 be used as a framework, because of its emphasis on non-cognitive changes. Since diagnosing Alzheimer's disease in Down's syndrome can be complicated, it is important to be thorough and comprehensive from the outset.

Assessment of the person with suspected dementia

Full psychiatric, personal, past medical and family histories and mental state assessment are essential. Attention should be paid to developmental, social and medication histories. The history should be

augmented by robust caregiver interviews, preferably with carers who observe the patient in different settings, although it should be remembered that informants might be unreliable. For example, a behaviour might be apparent in only one particular setting. It is important to compare the patient's current behaviour and functioning with that of the past (longitudinal history). This might involve contacting previous carers (family or institution based) if the individual is currently in supported living.

Predisposing factors should be identified, as in any psychiatric history, for example a history of head injury or stereotypical head banging might be a risk factor for dementia. Assessing the mental state is important to identify potential confounding factors such as primary psychiatric illness and treatable symptoms such as depression. The use of

Box 1 Symptoms of dementia in Down's syndrome

Cognitive

Forgetfulness of recent events (progressively long-term)
Geographical disorientation
Loss of previously learned skills
Confusion

Affective

Low mood
Insomnia/hypersomnia
Decreased concentration
Aggression and irritability
Anxiety and fearfulness
Loss of interest and anergia

Behavioural

Increased dependence
Social isolation
Excessive overactivity or restlessness
Excessive uncooperativeness
Personality change

Perceptual

Hallucinations in any modality

Neurological

Dysphasia leading to aphasia
Agnosia
Apraxia
Gait disturbance
Seizures
Myoclonus
Urinary incontinence
Dystonias
Loss of mobility

psychopathology checklists should be encouraged, as this should capture all symptoms present, not just those spontaneously reported by the patient or carers.

When interviewing individuals with Down's syndrome, consideration needs to be given to the fact that they may have a short attention span and may be suggestible, so that the answers they give are those that they think you want to hear. Open questioning, with frequent recapping, is therefore advised. There may be a discrepancy between the patients' understanding and how they express themselves, so that they may appear to understand more than they actually do. This may be partly due to the learning of various social phrases, which they appear to use appropriately. People with Down's syndrome may rely on gestures and facial expressions to help them understand the content of speech, and interviewers might need to accompany speech with gestures, signing or pictures.

It is important to establish current abilities and compare these with the patient's abilities at the best previous level of functioning, in order to identify any decline. Carers who have known an individual for only a short period may be unaware that skills have been lost and may attribute the current level of functioning to the learning disability. It is also important to try to establish the time course and progression of any deterioration, as this is important diagnostically. A diagnosis of depression rather than decline should be considered in the presence of fluctuating symptoms.

Test batteries for people with learning disabilities

For someone with suspected dementia, it is useful to include in an assessment test batteries to establish a baseline level of functioning. These tests can be repeated at intervals, which can be important when evaluating the progression of the dementia and a possible response to treatment. Tests would need to take into account the relatively low IQ range for people with Down's syndrome. For example, the Test for Severe Impairment (Modified) (Albert & Cohen, 1992) and the Spatial Recognition Span (Moss *et al*, 1986) require little or no speech. A useful scale is the Dementia Scale for Down's Syndrome (Gedye, 1995), as it is designed to measure early, middle and late stages of dementia. It includes the time course of the deterioration and a differential diagnosis scale. The Dementia Questionnaire for Persons with Mental Retardation (Evenhuis, 1996) has also gained prominence for use in this group. It is preferable that a clinical psychologist with experience in assessing people with learning disabilities performs

these tests. For further information on test batteries see Burt & Aylward (2000).

It is also important to test thoroughly for sensory impairment, because people with Down's syndrome may be unable to report such problems and it is these that determine which test batteries can be performed. Sensory deficits can also mimic cognitive impairment (Aylward *et al*, 1997). It is important to recognise both congenital and acquired sensory deficits, and this might require repeated testing over time.

Differential diagnosis

When approaching the diagnosis of dementia in Down's syndrome, it is of cardinal importance to rule out reversible causes of dementia and delirium. This is especially the case with hypothyroidism. This group of patients is particularly vulnerable to physical illness that causes cognitive decline. It is important to conduct a thorough physical and neurological examination. It should be kept in mind that neurological symptoms may present differently in this group. For instance, apraxia may present as an inability to dress or eat without assistance. Agnosia may present as the inappropriate use of everyday objects. Spatial disorientation may be evident from failures to locate familiar places in their environment. Box 2 summarises the differential diagnosis of dementia in Down's syndrome.

Box 2 Differential diagnosis of dementia in Down's syndrome

- Hypothyroidism
- Sensory loss
- Depression
- Sleep apnoea
- Cognitive decline secondary to medication (particularly anticholinergics)
- Delirium (multitude of causes)
- Chronic hepatitis
- Changes in environment, bereavement
- Alzheimer's disease
- Vascular dementia
- Dementia with Lewy bodies
- Neoplasms
- Folic acid abnormalities (patients taking anti-convulsants)
- Infection
- Other psychiatric disorders, e.g. anxiety and phobias
- Abuse

Box 3 Clinical investigations for dementia in Down's syndrome

Full blood count
 Urea and electrolytes
 Erythrocyte sedimentation rate and/or
 C-reactive protein
 Liver functions
 Thyroid functions
 Blood glucose
 Folate and B₁₂
 Computed tomography/magnetic resonance
 imaging of the brain
 Electrocardiogram
 Chest X-ray
 Electroencephalogram
 Plasma levels of drugs such as digoxin and anti-
 convulsants
 Mid-stream urine test
 Vision and hearing tests

Investigations for suspected dementia in Down's syndrome are listed in Box 3, although clinicians need to use their judgement as to what investigations an individual patient requires.

Structural imaging of the brain could be useful in Down's syndrome, although it is seldom diagnostic in its own right. It should be kept in mind that many people with Down's syndrome have abnormal scans. It is particularly useful for establishing the presence of vascular lesions, which aid in the differential diagnosis process. Studies using computed tomography (CT) scanning show cerebral atrophy in people with Down's syndrome and dementia. Temporal-lobe-oriented CT scans show reduction in volume in the medial temporal lobe (Lawlor *et al*, 2001). This may provide assistance in diagnosing Alzheimer's disease in Down's syndrome. It is known that in the general population, people who later develop Alzheimer's disease show atrophy in the medial temporal lobe. In Alzheimer's disease, neuronal loss in the hippocampus and amygdala is well recognised with reduced volumes on magnetic resonance imaging (MRI) scans (Aylward *et al*, 1999). Computed tomography scans may be better tolerated than MRI by individuals with learning disabilities, because of the claustrophobic nature of MRI scanning.

Management

When considering management of Alzheimer's disease in people with Down's syndrome it is important to take into account psychosocial and

physical factors. In the first instance, reversible causes of cognitive decline must be identified and corrected as far as possible. These include physical conditions such as delirium and hypothyroidism. Baseline assessment of functioning should be established for future reference.

Once a diagnosis of dementia is established it is useful to distinguish the type of dementia: Alzheimer's disease is the most common. In Down's syndrome, dementia with Lewy bodies may present differently from Alzheimer's disease. Depression, amotivational syndromes and psychotic symptoms may be more common in dementia with Lewy bodies (Simard & Van Reekum, 2001). Patients with dementia with Lewy bodies are particularly prone to adverse side-effects of psychotropic medication, especially typical antipsychotics, and atypicals may be better tolerated (Simard & Van Reekum, 2001).

Alzheimer's disease in Down's syndrome can present with cognitive, behavioural and psychiatric symptoms. It is important to target the symptoms being treated, so as not to exacerbate the patient's condition or cause harm through side-effects. People with learning disabilities are particularly prone to the side-effects of medication.

Increasingly, pharmacological treatment of the dementia is being considered. It is good practice in individuals with learning disabilities and dementia to try to avoid the prescription of anticholinergic agents, either alone or in combination. Individuals with dementia are vulnerable to exacerbations in their confusional states owing the anticholinergic effects of many psychiatric drugs. It would be advisable, in the first instance, to treat depression with a selective serotonin reuptake inhibitor, as tricyclics are anticholinergic. Psychosis should be treated with antipsychotics and, as mentioned above, it is preferable to use atypical agents, owing to their better side-effect profile and the association between Down's syndrome and dementia with Lewy bodies. Clinicians should always endeavour to use drugs with the fewest side-effects, as people with learning disabilities may find it difficult to report adverse effects and may have multiple additional physical conditions. The behavioural and psychological symptoms of dementia, although preferably handled by non-pharmacological means, can be treated as recommended for the general adult population (Bouman & Pinner, 2002).

Psychological assessment can be very useful, both in identifying possible causes of behavioural changes and in providing advice for their management. Carbamazepine has been shown to be beneficial in agitation and aggression and benzodiazepines can also be used, bearing in mind the potential risks of oversedation, falls and tolerance.

Treatment of dementia in Down's syndrome

Direct treatment of the dementia itself remains controversial in Down's syndrome. There has been limited research showing that donepezil, an acetylcholinesterase inhibitor, is effective in slowing the decline of functional ability in Alzheimer's disease, but at this stage it is uncertain whether similar gains could be achieved in Alzheimer's disease associated with Down's syndrome. There has been some evidence that these agents may be useful in this group of patients (Prasher *et al*, 2002; Kishnani *et al*, 2001), although there have also been concerns that they may be poorly tolerated (Hemingway-Eltomey & Lerner, 1999).

The consensus at present appears to be that acetylcholinesterase inhibitors should be considered and that a very slow titration of the dose should be the norm (e.g. 5 mg donepezil daily for 4–6 weeks before increasing the dose). It is known that optimum benefits are gained from maximising the dose of acetylcholinesterase inhibitors. Donepezil appears to be the only acetylcholinesterase inhibitor that has been systematically evaluated in Down's syndrome, but galantamine and rivastigmine are also available.

It should be noted that acetylcholinesterase inhibitors are not licensed specifically for use in people with a learning disability. However, this is the case for many psychotropic agents, usually because learning disability is frequently an exclusion criterion for clinical trials (Fraser, 1999). The contraindications for acetylcholinesterase inhibitors are listed in Box 4.

Physical and psychosocial factors

Psychosocial interventions form a large part of the management of dementia in Down's syndrome. Safety and stability of the individual's environment are of the utmost importance. It has been shown that the level of cognitive function has the greatest association with decline and that, in turn, environmental factors have the greatest impact on cognitive function (Temple *et al*, 2001). It might therefore hold true that environmental interventions increase cognitive function, which in turn might ameliorate the progression of the dementia.

The decision to move or not to move should be carefully considered. Stability in the environment helps to reduce confusion, and therefore carers and location should not readily be changed. It is recommended that individuals be maintained in their present environment for as long as is safely possible. Conversely, if they do have to be moved, they are more likely to adapt to their new environment if this is done earlier, while they retain

more cognitive function. It is also important to remember that families caring for people with Down's syndrome and Alzheimer's disease may find it very difficult to consider moving them into residential care, owing to feelings of guilt. Carers must be supported when this decision has to be made.

Minimising their sensory deficits allows people with dementia to remain in their current environment for as long as possible, by maximising their ability to orient themselves and to communicate effectively with their carers. Strategies to support and maintain the strengths of the individual are important and may necessitate modifications to the environment. It can be helpful to encourage participation in as many activities as possible, although it is important that these do not exceed the individual's abilities, as that might result in frustration and apparent decline in functioning. Regular small changes are preferable to infrequent large ones. Regular medical review can be helpful for monitoring mental state, thyroid and cardiac status, infections, anaemias and deteriorating sensory function, so that any abnormalities found can be treated.

Box 4 Cautions and contraindications of acetylcholinesterase inhibitors in dementia

Cautions

- Cardiac conduction abnormalities
- Peptic ulceration
- Urinary hesitancy and bladder outflow obstruction
- Chronic obstructive pulmonary disease and asthma
- Hepatic impairment
- Gastrointestinal obstruction
- Renal impairment

Contraindications

- Pregnancy and breast-feeding
- Gastrointestinal bleeding

Drug interactions

- Antipsychotics, including chlorpromazine, clozapine, olanzapine and thioridazine, because of their anticholinergic profile
- Antidepressants, including the tricyclics, paroxetine, fluoxetine, monoamine oxidase inhibitors
- Anticholinergics, including procyclidine, benztropine, trihexyphenidyl/benzhexol, orphenadrine, hyoscine
- Suxamethonium
- Non-depolarising muscle relaxants

Attention should also be paid to the needs of carers, to reduce carer burden. Carers and family members sometimes report that they feel isolated and fearful of the likely impact of dementia on an individual with Down's syndrome. Consideration of the psychological and practical needs of carers is vital. It is important to ensure good communication at every stage, and professionals might need to anticipate carers' questions and concerns. Provision of written information on commonly encountered problems in dementia might be helpful for carers, as might putting them into contact with the Alzheimer's Society (tel: 020 7306 0606; website: <http://www.alzheimers.org.uk>) or the Down's Syndrome Association (tel: 020 8682 4001; website: <http://www.downs-syndrome.org.uk>).

Members of the community learning disability team can provide advice for managing problems, and other members of the multi-disciplinary team also give important support. Physiotherapists can assist in mobility issues, and occupational therapists in rehabilitation and preservation of skills. Nursing staff (especially within the community learning disability team) have a great deal to offer from the outset, but their role becomes more pronounced as dementia progresses and nursing care becomes more central. It is important also to consider day care facilities or in-patient admission, but it should be remembered that moving the person into residential care might hasten functional decline and should be considered a last resort.

Prognosis

The prognosis for dementia in general is poor and the presence of Down's syndrome further complicates the situation. However, it should be kept in mind that many people with dementia, with or without Down's syndrome, lead full and meaningful lives despite cognitive decline. But dementia is usually a progressive illness, and eventually it overtakes most people because of its complications. In the final stages, the individual's physical health needs may become paramount and require specialist care, which may include palliative care. The aim of treatment at present involves slowing of and adaptation to decline, containment of distress and symptom relief rather than attempts to cure or reverse the condition. This means encouraging continued social and occupational activities in keeping with the individual's changing abilities. Most patients die from the physical complications of dementia such as respiratory tract infection and thromboembolism (Evenhuis, 1990).

Future developments

Several authors have suggested that baseline cognitive testing would be helpful for people with Down's syndrome when they reach early adulthood. It would be advisable to ensure consensus on which test batteries are used. Early adulthood has been suggested for baseline assessment, as people with learning disability often continue to develop well into adulthood, and it is important to ensure that the optimum level of achievement has been attained when establishing a baseline. If baseline testing were to become more widespread this would make it easier to identify decline if dementia is suspected later in life.

Much more research is needed in this field, especially in the treatment of Alzheimer's disease in Down's syndrome. Possible sites for intervention in Alzheimer's disease include enhancement of cholinergic neurotransmission, neurotransmitter substitution or modulation, modulation of amyloid precursor protein processing, reduction of tau hyperphosphorylation, ApoE modulation, modulation of glutamergic neurotransmission and the use of neuronal growth factors.

There is research ongoing that will investigate the usefulness of anti-inflammatory drugs, oestrogen and secretase inhibitors (which may prevent β -amyloid deposition, and hence halt progression of Alzheimer's disease). Vitamins C and E, which are antioxidant, are being evaluated, and immunisation therapies may be on the horizon. Ampakines, which are active at excitatory amino acid (glutamate) receptors, may enhance synaptic response, possibly by slowing deactivation. Piracetam, a nootropic, is being evaluated as a drug that might improve cognitive impairment.

The new addition of memantine (an *N*-methyl-D-aspartate receptor antagonist) for the treatment of moderate to severe Alzheimer's disease in the general population may very well spread to use in Alzheimer's disease associated with Down's syndrome. Initial data on elderly people show that memantine can bring benefits in activities of daily living and cognition, although evidence is at present scanty.

There is already work ongoing into the prophylactic use of acetylcholinesterase inhibitors in people with Down's syndrome and Alzheimer's disease, but more extensive evaluation of their use in this group will be required in the future. In particular, multi-centre randomised controlled trials with prolonged periods of follow-up are needed to evaluate their effectiveness in Down's syndrome.

Genetic screening for Alzheimer's disease has already been carried out successfully in the USA, and it seems likely that improvements in this technology will bring into clinical practice genetic screening for Alzheimer's disease in Down's syndrome. Gene therapy and stem-cell transplantation are also being evaluated, but any effective clinical treatment is still some way off.

References

- Albert, M. & Cohen, C. (1992) The test for severe impairment: an instrument for the assessment of patients with severe cognitive dysfunction. *Journal of the American Geriatric Society*, **40**, 449–453.
- Aylward, E. H., Burt, D. B., Thorpe, L. U., *et al* (1997) Diagnosis of dementia in individuals with intellectual disability. *Journal of Intellectual Disability Research*, **41**, 152–164.
- Aylward, E. H., Li, Q., Honeycutt, N. A., *et al* (1999) MRI volumes of the hippocampus and amygdala in adults with Down's syndrome with and without dementia. *American Journal of Psychiatry*, **156**, 564–568.
- Bouman, W. P. & Pinner, G. (2002) Use of atypical antipsychotic drugs in old age psychiatry. *Advances in Psychiatric Treatment*, **8**, 49–58.
- Burt, D. B. & Aylward, E. H. (2000) Test battery for the diagnosis of dementia in individuals with intellectual disability. *Journal of Intellectual Disability Research*, **44**, 175–180.
- Cooper, S. A. & Prasher, V. P. (1998) Maladaptive behaviours and symptoms of dementia in adults with Down's syndrome compared with adults with intellectual disabilities of other aetiologies. *Journal of Intellectual Disability Research*, **42**, 293–300.
- Cosgrave, M. P., Tyrrell, J., McCarron, M., *et al* (2000) A five year follow-up study of dementia in persons with Down's syndrome: early symptoms and patterns of deterioration. *Irish Journal of Psychological Medicine*, **17**, 5–11.
- Evenhuis, H. M. (1990) The natural history of dementia in Down's syndrome. *Archives of Neurology*, **47**, 263–267.
- Evenhuis, H. M. (1996) Further evaluation of the Dementia Questionnaire for Persons with Mental Retardation (DMR). *Journal of Intellectual Disability Research*, **40**, 369–373.
- Fraser, B. (1999) Psychopharmacology and people with learning disability. *Advances in Psychiatric Treatment*, **5**, 471–477.
- Gedye, A. (1995) *Dementia Scale for Down's Syndrome. Manual*. Vancouver, BC: Gedye Research and Consulting.
- Hemingway-Eltomey, J. M. & Lerner, A. J. (1999) Adverse effects of donepezil in treating Alzheimer's disease associated with Down's syndrome. *American Journal of Psychiatry*, **156**, 1470.
- Holland, A. J., Hon, J., Huppert, F. A., *et al* (1998) Population-based study of the prevalence and presentation of dementia in adults with Down's syndrome. *British Journal of Psychiatry*, **172**, 493–498.
- Holland, A. J., Hon, J., Huppert, A., *et al* (2000) Incidence and course of dementia in people with Down's syndrome: findings from a population-based study. *Journal of Intellectual Disability Research*, **44**, 138–146.
- Kishnani, P. S., Spiridigliozzi, G. A., Heller, J. H., *et al* (2001) Donepezil for Down's syndrome (comment). *American Journal of Psychiatry*, **158**, 143.
- Lawlor, B. A., McCarron, M., Wilson, G., *et al* (2001) Temporal lobe-oriented CT scanning and dementia in Down's syndrome. *International Journal of Geriatric Psychiatry*, **16**, 427–429.
- Mann, D. M., Iwatsubo, T., Ihara, Y., *et al* (1996) Predominant deposition of amyloid-beta 42(43) in plaques in cases of Alzheimer's disease and hereditary cerebral haemorrhage associated with mutations in the APP gene. *American Journal of Pathology*, **148**, 1257–1266.
- Moss, M. B., Albert, M. S., Butters, N., *et al* (1986) Differential patterns of memory loss among patients with Alzheimer's disease, Huntington's disease, and alcoholic Korsakoff's syndrome. *Archives of Neurology*, **43**, 239–246.
- Oliver, C., Crayton, L., Holland, A., *et al* (1998) A four year prospective study of age-related cognitive change in adults with Down's syndrome. *Psychological Medicine*, **28**, 1365–1377.
- Prasher, V. P., Huxley, A. & Haque, M. S. (2002) A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Down syndrome and Alzheimer's disease. Pilot study. *International Journal of Geriatric Psychiatry*, **17**, 270–278.
- Rabe, A., Wisniewski, K. E., Schupf, N., *et al* (1990) Relationship of Down's syndrome to Alzheimer's disease. In *Application of Basic Neuroscience to Child Psychiatry* (eds S. I. Deutsch, A. Weizman & R. Weizman), pp. 325–340. New York: Plenum Press.
- Reiss, S., Levitan, G. W. & Szyszko, J. (1982) Emotional disturbance and mental retardation: diagnostic overshadowing. *American Journal of Mental Deficiency*, **86**, 567–574.
- Royal College of Psychiatrists (2001) *DC-LD [Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities/Mental Retardation]* (Occasional Paper OP48). London: Gaskell.
- Schupf, N. (2002) Genetic and host factors for dementia in Down's syndrome. *British Journal of Psychiatry*, **180**, 405–410.
- Schupf, N., Kapell, D., Nightingale, B., *et al* (2001) Specificity of the fivefold increase in Alzheimer's disease in mothers of adults with Down syndrome. *Neurology*, **57**, 979–984.
- Seltzer, G. B., Schupf, N. & Wu, H. S. (2001) A prospective study of menopause in women with Down syndrome. *Journal of Intellectual Disability Research*, **45**, 1–7.
- Simard, M. & Van Reekum, R. (2001) Dementia with Lewy bodies in Down's syndrome. *International Journal of Geriatric Psychiatry*, **16**, 311–320.
- Temple, V., Jozsvai, E., Konstantareas, M. M., *et al* (2001) Alzheimer dementia in Down's syndrome: the relevance of cognitive ability. *Journal of Intellectual Disability Research*, **45**, 47–55.
- Tyrell, J., Cosgrave, M., McCarron, M., *et al* (2001) Dementia in people with Down's syndrome. *International Journal of Geriatric Psychiatry*, **16**, 1168–1174.
- Visser, F. E., Aldenkamp, A. P., Van Huffelen, A. C., *et al* (1997) Prospective study of the prevalence of Alzheimer-type dementia in institutionalized individuals with Down syndrome. *American Journal on Mental Retardation*, **101**, 400–412.
- Wisniewski, K. E., Wisniewski, H. M. & Wen, G. Y. (1985) Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Annals of Neurology*, **17**, 278–282.

Multiple choice questions

1 People with Down's syndrome:

- are at risk of developing early-onset Alzheimer's disease
- are at risk of developing dementia with Lewy bodies
- have senile plaques in middle age
- do not have neurofibrillary tangles in middle age
- have mothers with an increased risk of Alzheimer's disease.

2 As regards β -amyloid:

- a it is formed by cleavage of amyloid precursor protein
- b it is cleaved to form AB1-40
- c it is cleaved to form AB1-42
- d in the AB1-42 form it is implicated in the onset of Alzheimer's disease
- e mutations in the amyloid precursor protein gene causing β -amyloid deposition are implicated in the pathogenesis of familial Alzheimer's disease.

3 Difficulties in diagnosing dementia in Down's syndrome:

- a can be due to psychosocial masking
- b can be reduced by diagnostic overshadowing
- c can be due to impaired communication skills
- d may be complicated by baseline exaggeration
- e can be reduced by intellectual distortion, which helps in identifying subjective symptoms.

4 Affective symptoms of Alzheimer's disease in Down's syndrome include:

- a low mood
- b insomnia
- c poor concentration
- d irritability
- e anergia.

5 Cautions for acetylcholinesterase inhibitors include:

- a cardiac conduction abnormalities
- b hypothyroidism
- c hepatic impairment
- d peptic ulcer
- e bladder outflow obstruction.

MCQ answers

1	2	3	4	5
a T	a T	a T	a T	a T
b T	b T	b F	b T	b F
c T	c T	c T	c T	c T
d F	d T	d T	d T	d T
e T	e T	e F	e T	e T

Young People and Substance Misuse

Edited by Ilana Crome, Hamid Ghodse, Eilish Gilvarry and Paul McArdle

Substance misuse is one of the most common and serious yet preventable risks to a young person's health and development. This book provides an overview of the consequences of substance misuse, the interventions and services available, and, most importantly, the way forward for improving treatment and services. *Young People and Substance Misuse* brings international expertise together with a UK health care perspective. It will give the reader an in-depth understanding of the issues as well as suggesting practical solutions to a problem that affects so many aspects of the well-being of teenagers.

This is a book for all those who need to know more about the options for prevention and treatment – teachers, carers, parents, researchers and policy-makers as well as those working in the criminal justice system, social services and mental health care.

- The book includes expert analysis of:
- Prevalence and routes to drug use
 - Misuse of illicit drugs, alcohol and tobacco
 - Parental, family and social influences
 - Treatment and prevention strategies

Due December 2003, Paperback, 240pp, ISBN 1 904671 01 2, Price £15.00



TO ORDER PLEASE CONTACT:

Book Sales, Royal College of Psychiatrists, 17 Belgrave Square, London SW1X 8PG, UK.
Tel: +44 (0)20 7235 2351 ext 146. Fax: +44 (0)20 7245 1231.
Online ordering at: www.rcpsych.ac.uk/publications