Down Syndrome and Alzheimer's Disease

Biological Correlates

Edited by Vee P Prasher ◆ Foreword by Trevor Parmenter

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To Dr Vallepur HR Krishnan, Consultant in Developmental Psychiatry,
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Foreword

In the century 1850–1950 scientific inquiry into intellectual disability was essentially characterised by a focus on the physical characteristics of people with this diagnosis, including those with Down syndrome. In 1866 Langdon Down, after whom the syndrome was named, reported that the physical features of many of his patients at London Hospital and the Earlwood Asylum resembled the Mongolian race. He also pointed out that the condition appeared to cross racial boundaries. Concerning possible aetiology, he suggested that it was inherited from tuberculosis in the parents. It was not until 1959 that Lejeune and colleagues made the discovery that the extra chromosome was the underlying cause of Down syndrome.

In general terms, the last half of the twentieth century witnessed a major shift away from the "medical" model of disability which had sought to describe, diagnose, classify and treat impairments; to an emphasis upon the "social" model that grew out of a combination of philosophical, advocacy and human rights movements. Many condemned the medical model for its supposed pessimism about the educability of people with an intellectual disability, but significantly Langdon Down reported on the positive effects of training as did Seguin before him.

The "schism" between the medical and social models to some extent became evident in the world congresses of the International Association for the Scientific Study of Intellectual Disabilities (IASSID) where there was a polarisation of two distinctive themes; one exploring traditional medical aspects and the other concentrating upon community living and social aspects of the lives of people with an intellectual disability. The emergence of Special Interest Research Groups (SIRGs) in the 1990s, spearheaded by the Ageing SIRG, has significantly helped to integrate the medical and social aspects of scientific inquiry. The issue of the early onset of dementia in adults with an intellectual disability, especially those with Down syndrome, has been a special focus of the work of this group.

The publication of this book, which brings together in one volume major biological aspects concerning dementia in Alzheimer's disease (DAD) in adults with Down syndrome, is particularly significant for at least three reasons. First, the very biological bases underpinning the development of dementia in Alzheimer's disease provide an important bridge between basic research in the general population and that in the area of Down syndrome and in intellectual disability generally. This provides an excellent opportunity for a cross fertilisation of efforts. Not only is dementia in Alzheimer's disease emerging as the greatest challenge for those charged with the health and community care of people who are ageing with an intellectual disability; it is a similar challenge for the dramatically increasing numbers of older people in the general population. It is somewhat ironic that whilst better healthcare and improved life style (at least in the developed world) has lengthened life expectancy for all, society is being challenged by the possibility of the increased exposure of the ageing population to disease and disability.

Second, it provides a comprehensive "state of the art" analysis of the biological correlates of DAD and Down syndrome from a variety of scientific perspectives including genetics, biochemistry, neurophysiology, neuropathology, neuropsychiatry and neuroimaging.

Third, this analysis also provides a clear indication as to where future research efforts need to be targeted, especially in the development of reliable markers that might improve clinical diagnostic accuracy and assist early detection. Presently the clinical diagnosis of DAD is fraught with imprecision and, even when accurate, may be made at the end of a long process of hidden neuropathology.

The scientific community investigating one of the most serious health challenges facing adults with an intellectual disability is indebted to Dr Vee Prasher and colleagues for this scholarly contribution to the study of the biological correlates of dementia in Alzheimer's disease in adults with Down syndrome. This important collection of the most recent research findings in this field of enquiry will further stimulate efforts to develop treatments that may ameliorate the condition; delay its onset, and ultimately provide means for prevention.

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Preface

To fully appreciate the recent advances in the clinical and cognitive aspects of dementia in Alzheimer's disease (DAD) in adults with Down syndrome, an awareness of the essential biological aspects underlying the disease process is essential. Furthermore, in view of a number of significant developments in our knowledge of basic brain mechanisms and in aspects of neuroscience affecting Alzheimer's disease in the general population, it is important that a resource is made available which critically appraises the important biological aspects of DAD in older adults with Down syndrome. This book aims to provide for researchers and clinicians in the field of intellectual disability a resource on recent neuropsychiatric developments in Alzheimer's disease which may supplement existing clinical knowledge.

This book endeavours to bring together in one place recent research findings relating to the neuropathology, genetics, blood markers and neurophysiological aspects of Alzheimer's disease in older adults with Down syndrome. To date, the majority of interest in this area has been focused on the clinical and diagnostic aspects of DAD in the intellectually disabled population. Until recently the underlying biological abnormalities, which possibly give rise to the clinical psychopathology of DAD in individuals with Down syndrome, have been neglected. To our knowledge this book is the first in the field of intellectual disability to have been published in order to address this concern.

The overall goal of this book is to help researchers and clinicians working with people with intellectual disability to better understand the biomedical abnormalities of DAD, and to facilitate interest and further research into the fundamentals of Alzheimer's disease in adults with Down syndrome.

A few comments are needed on the terminology adopted in this text. The term 'Alzheimer's disease' has been used to denote the neuropathological disease process, while 'dementia in Alzheimer's disease' has been used to refer to the clinical aspects of the neurodegenerative condition. It is accepted that such terms have not yet gained universal acceptance. In addition, the term 'intellectual disabilities' is used to denote what the International Association for the Scientific Study of Intellectual Disabilities (IASSID) refers to as intellectual disability. This term is used synonymously with 'mental retardation', 'learning disabilities', 'mental handicap' and 'intellectual handicap.'

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About the editor

Vee P Prasher is a Consultant Psychiatrist in Neurodevelopmental Psychiatry in Birmingham and a Senior Research Fellow at King's College London. He graduated from Birmingham University in 1985 and has subsequently completed MMedSci, MD and PhD postgraduate degrees. His main research interests are ageing and the physical health of adults with Down syndrome. He has published over 100 research articles and edited or written a number of textbooks on intellectual disabilities. In 2004 he was conferred the title of Fellow of the International Association for the Scientific Study of Intellectual Disabilities.

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List of abbreviations

Aβ	amyloid β-peptide
ABS	adaptive behavior scale
AChE	acetylcholinesterase
ACT	α-1-antichymotrypsin
ACTH	adrenocorticotropic hormone
AD	Alzheimer's disease
AEP	auditory evoked potential
ApoE	apolipoprotein E
APP	amyloid precursor protein
BACE	beta-site amyloid precursor protein-cleaving enzyme
CAMDEX	Cambridge Examination for Mental Disorders of the Elderly
ChAT	choline acetyltransferase
CRH	corticotrophin-releasing hormone
Cr+PCr	creatine and phosphocreatine
CSF	cerebrospinal fluid
CT	computerised tomography
DAD	dementia in Alzheimer's disease
DMR	Dementia Questionnaire for Mentally Retarded Persons
DS	Down syndrome
DSDS	Dementia Scale for Down Syndrome
DSM–III	*Diagnostic and Statistical Manual of Mental Disorders – Third Edition*
DSM–IV	*Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition*
ECF	extracellular fluid
EEG	electroencephalography
ELISA	enzyme-linked immunosorbent assay
FAD	familial form of Alzheimer's disease
HDL	high-density lipoprotein
^{1}H-MRS	proton magnetic resonance spectroscopy
HPT	hypothalamic–pituitary–thyroid axis
HSPG	heparan sulphate proteoglycan
ICD–9	*International Classification of Diseases and Related Health Problems – Ninth Revision*
ICD–10	*International Classification of Diseases and Related Health Problems – Tenth Revision*
ID	intellectual disability
LDL	low-density lipoprotein
LOMEDS	late-onset myoclonic epilepsy in adults with Down syndrome
MCI	mild cognitive impairment
MCV	mean corpuscular volume
MDT	multi-disciplinary team
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging

NAA	*N*-acetylaspartate
NFT	neurofibrillary tangles
NSF	National Service Framework
PET	positron emission tomography
PHF	paired helical filaments
PS1	presenilin 1
PS2	presenilin 2
rCBF	regional cerebral blood flow
SIB–R	Scale of Independent Behaviour – Revised
SOD1	superoxide dismutase-1
SP	senile plaques
SPECT	single photon emission computed tomography
T3	triiodothyronine
T4	thyroxine
TBG	thyroxine-binding globulin
TBP	thyroxine-binding proteins
Tg	thyroglobulin
TRH	thyroid-releasing hormone
TSH	thyroid-stimulating hormone
VBM	voxel-based morphometry
VEP	visual evoked potential
VLDL	very-low-density lipoprotein

Chapter 1

Overview of Alzheimer's disease in Down syndrome

Robert J Pary, Gautam Rajendran and Andrea Stonecipher

Introduction

It may seem strange, but there is good news about people with Down syndrome (DS) being at risk for Alzheimer's disease (AD). A century ago, babies with DS seldom lived long enough to develop AD! In the early twentieth century the average lifespan of a child with DS was 9 years.[1] Just over two decades ago, the median age of death for people with DS was 25 years.[2] At the start of the new millennium the average life expectancy is now only 15–20 years less than that for the general population.

In contrast to the many books and articles written by and for parents about the experience of raising a child with DS, very little has been written about the personal experience of families in dealing with a family member who has both DS and dementia in Alzheimer's disease (DAD). It was not until the last decade of the twentieth century that texts written specifically for parents of people with DS began to include the issue of dementia.[3] Family accounts are now being published. Margaret T Fray has written about the challenging experience of caring for her sister with DS and dementia.[4] Unfortunately, Fray's book is not readily accessible in many countries.

As a result of medical advances, it is now common for a person with DS to live to over 60 years of age.[5] In contrast to the general population, men with DS live longer than women with DS. In 2000, the median life expectancy was 61.1 years for men and 57.8 years for women.[6] Furthermore, not everyone with DS develops DAD, although the risk is considerable. Some service planners are beginning to believe that the actual numbers of people with DS and DAD may be lower than was previously thought, although they are still quite substantial.[7] Approximately 50–60% of adults with DS will develop DAD by the age of 60 to 70 years.[8] However, there are case reports in the literature of elderly individuals with DS but without DAD.

Chicoine and McGuire[9] describe the case of 'Ann', an 83-year-old woman with DS. On physical examination, she had several characteristic features of DS, including a flattened occiput, eyelids that slanted upward, prominent epicanthal folds, Brushfield spots (mottled or speckled areas on the iris), small palate, bilateral valgus-curving of the fifth finger, small hands and small feet. Furthermore, she had health problems commonly associated with DS, including bilateral hallux valgus, bilateral cataracts, and dystrophic toenails with onychomycosis. Chromosome analysis revealed mosaic 21 (75% had trisomy 21 and 25% were

normal). 'Ann' died one month after suffering a hip fracture. Prior to death she had not shown signs of dementia, such as loss of memory or loss of skills (except those explained by the hip fracture).

However, whatever 'positive spin' one gives the increased risk of AD in individuals with DS soon disappears when the reality of DAD hits, as it did in the case of Margaret T Fray's sister.[4] Alzheimer's disease robs a person of his or her connection to loved ones and eventually to him- or herself.

History of dementia and Down syndrome

Functional deterioration in adults with DS has been noted since the nineteenth century. In 1876, Fraser and Mitchel[10] wrote that individuals with DS had a 'sort of precipitated senility.' As was mentioned above, a century ago few children with DS survived to teenage years. It is therefore somewhat surprising that post-mortem evidence of AD in an adult with DS was described as early as 1929[11] according to Lott.[12] In the mid-twentieth century, Jervis was the first clinician to suggest that AD complicates ageing in older adults with DS.[13]

One of the seminal observations of recent history has been the detection of AD neuropathology (senile plaques and neurofibrillary tangles) in the brains of adults with DS who are older than 35 years.[14] The belief in the inevitability of AD changes in the post-mortem brains of adults with DS significantly affected the way in which clinicians, carers and family members approached the ageing process of older adults with DS in the 1980s and 1990s. Furthermore, prevalence studies became extremely important, and will be discussed in detail. The neuropathology of AD in people with DS will be discussed in Chapter 2 of this book.

Epidemiology of dementia in individuals with Down syndrome

Accurate information about the prevalence (i.e. the total number of cases) of DAD in DS is critical if erroneous clinical attitudes are to be avoided. A 1994 international conference concluded that 'estimates of overall and age-specific rates of Alzheimer-type dementia in adults with DS . . . vary widely (from under 10% to over 75%).'[15] However, an article published within the past decade still referred to the inevitability of DAD in individuals over 40 years of age with DS. Martin[16] advised that 'early AD occurs in almost 100% of DS patients over 40 years old.' Smith[17] argued forcefully against this pessimistic view in a Letter-to-the-Editor response to Martin's article. Martin did recommend ruling out reversible causes first. However, clinicians who believe in the inevitability of DAD in people over 40 years of age with DS will probably fail to search aggressively for potential reversible causes of the decline.

There are several methodological challenges in accurately determining the epidemiology of dementia in individuals with DS. One fundamental difficulty is that some studies use phenotypic rather cytogenetic diagnosis of DS.[18] The problem with using phenotypic criteria alone for the diagnosis of DS has been highlighted previously,[19] and became apparent to one of the authors (RJP) during a psychiatric consultation. The individual concerned was 45 years old and had

been diagnosed with DS during infancy by her family doctor. She had short stature, intellectual disability (ID) and an upward slant to her eyes (she was of Asian descent). However, she did not have a palmar crease, Brushfield spots, flattened occiput, valgus-angled fifth finger or a space between her first and second toes. What was most suspicious of all was that she looked at least ten years younger than her chronological age. Her middle-class, college-educated family never questioned the diagnosis of DS, and karotyping was never undertaken. Although the individual had several behavioural challenges, none of them would lead one to suspect dementia or a behavioural phenotype of DS.

Although lack of chromosomal confirmation can be problematic in large population surveys, there are other potential limitations. Bush and Beail[20] discussed several other methodological issues in accurately determining the prevalence of dementia in people with DS, including cohort bias in cross-sectional designs, the lack of a standardised protocol to rule out potentially reversible causes of functional decline, non-standardised diagnostic criteria and inadequate evaluations of premorbid cognitive functioning. Cohort bias in cross-sectional designs refers to two potential problems. One is the problem of conducting prevalence studies exclusively using subjects living in an institution. The lack of educational, cultural or vocational stimulation in an institution can result in individuals appearing regressed.[21] Similarly, the shock of being admitted to an institution, especially if someone has lived all of one's life prior to this at home, could cause a temporary regression in functioning. A cross-sectional study would only report a decline. In addition, as Bush and Beail[20] emphasise, some individuals may be admitted to an institution while in the very early stages of dementia. All of these factors can result in overestimation of the prevalence rates of DAD in adults with DS living in an institution. If individuals with DS in a longitudinal study die from non-dementia-related causes, the surviving cohort may be skewed.[20] This means that as members of the cohort group die, but never developed dementia, the percentage (and significance) of those survivors who do develop dementia may be unduly increased.

Another major issue in some studies has been the lack of a standardised protocol to eliminate other causes of functional decline. The differential diagnosis of dementia in DS will be covered in detail later. Bush and Beail[20] point out that some early researchers assumed that any functional decline in older adults with DS had to be due to AD. Cross-sectional studies would be at increased risk for this kind of error.

A third major problem is the use of non-standardised diagnostic criteria for dementia in individuals with DS.[20] Some researchers will estimate different odds ratios of dementia according to how stringently the diagnostic criteria for dementia are defined. Zigman and colleagues studied 2534 people with DS and 16 182 people with ID due to other causes,[18] and found significantly different rates depending on the strictness of the criteria for dementia.

One solution to the lack of standardised diagnostic criteria has been the formation of an international Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Intellectual Disability.[22] This working group endorsed a test battery that included a number of different scales. Some tests which could be used as part of the test battery include (i) the Dementia Questionnaire for Mentally Retarded Persons (DMR),[23] (ii) the Dementia Scale for Down Syndrome (DSDS),[24] (iii) the Reiss Screen[25] Scale of Independent

Behaviour–Revised (SIB–R)[26] and (iv) the Adaptive Behaviour Scale.[27] These scales were just the ones administered to informants. In addition, there were 11 other scales to be administered to the individual! Unfortunately, the battery is too unwieldy for clinical work (as well as for most research studies). The proposed test battery is a worthy preliminary endeavour, but is in need of 'pruning' before it can be widely used in the field.

A recent multi-centre evaluation of screening tools for dementia in older adults with ID (including 26 out of 38 individuals with DS) did not use the working group's complete test battery (although it did use parts of it).[28] Schultz and colleagues[28] concluded that there is still not a 'gold standard', although they found both the DSDS[24] and the DMR[23] useful.

With the above-mentioned cautions, the following are several representative prevalence studies of DS and AD. Lai[29] describes findings representative of prevalence studies in institutionalised individuals with DS. Lai's group followed 53 individuals with DS over the age of 35 years, and found that 6% had dementia in the 35–49 years age cohort, 55% in the 50–59 years cohort and 100% in the cohort aged 60 years or over (an earlier report from the group had estimated the prevalence in people over 60 years of age to be 75%).

In contrast, a study by Sekijima and colleagues of institutionalised adults with DS in Japan found a lower prevalence.[30] They described 106 individuals who were 30 years or older. The number of individuals who were diagnosed clinically with DS compared with the number for whom confirmation was obtained with chromosomal analysis was not given. None of the 39 individuals aged 30 to 39 years had dementia. Among those aged 40 to 49 years, 7 out of 43 (16%) had dementia, and among those aged 50 to 59 years, 9 out of 22 (41%) had dementia. Neither of the two individuals aged over 60 years had dementia.

Visser and colleagues[31] followed 307 patients with DS who were monitored for 5 to 10 years prospectively in order to determine the prevalence of DAD in an institutionalised setting. Clinical signs, cognitive functioning and electroencephalograms were assessed. Whenever possible, post-mortem neuropathological examinations were performed. Progressive mental and physical deterioration was found in 56 of the institutionalised patients. The mean age at onset of dementia was 56 years. The prevalence increased from 11% between the ages of 40 and 49 years to 77% between the ages of 60 and 69 years, and all patients over 70 years of age had dementia. Visser's group[31] reported that the neuropathological findings were consistent with the clinical diagnosis.

Future prevalence studies will not only need to include chromosomal analysis of all of the participants, but will also need to determine whether the karyotype was atypical. Some reports are already providing numbers of atypical karyotypes.[32] Schupf[33] notes mosaicism in both 'Ann', the 83-year-old woman with DS described by Chicoine and McGuire,[9] and a 74-year-old woman without dementia. 'Ann' had 25% disomy for chromosome 21, and the 74-year-old woman without signs of DAD had 86% disomy. Schupf[33] believes that atypical karyotypes, such as translocations, partial trisomies and mosaicism, may have a lower risk for AD.

Introduction to the genetics of Alzheimer's disease and Down syndrome

The increased risk of AD in DS is attributed to a gene found on chromosome 21, for *amyloid precursor protein (APP)*, although the trigger for development of dementia is unknown.[33] APP has three copies in DS because of trisomy 21. Amyloid is accumulated extracellularly in senile plaques, a characteristic feature of the neuropathology of AD. APP is cleaved by proteases, β- and γ-secretase.[34] A product of APP is the amyloid β-peptide, Aβ1–42, which is selectively increased in early-onset familial AD.[34] Amyloid β-peptide can be measured in the plasma. Schupf and colleagues[35] noted that levels of the amyloid peptides Aβ1–42 and Aβ1–40 were higher in adults with DS than in controls. In the general population, elevated plasma Aβ1–42 levels may indicate an increased risk of AD.[36] (For further details on the association between amyloid and AD in DS, *see* Chapters 3 and 4.) Another gene of interest on chromosome 21 is that for superoxide dismutase-1 (SOD1).[37] SOD1 consists of 154 amino acids and is involved in oxygen metabolism.[38] (For further information on SOD1 and AD in DS, *see* Chapter 5.)

Although it does not occur on chromosome 21, an apolipoprotein E (ApoE) genotype is associated with AD.[39] ApoE appears to be involved in the transportation of cholesterol. There are three alleles, namely ϵ2, ϵ3 and ϵ4. Research investigating ApoE and AD in individuals with DS has not yielded consistent findings, but according to Schupf[33] the ApoE ϵ4 allele appears to be associated with an earlier onset of dementia. In contrast, ApoE ϵ2 offers some protection and is associated with a reduced risk of dementia. This topic is covered in detail in Chapter 3.

Natural history of dementia in individuals with Down syndrome

A study by Thase and colleagues[40] was one of the first to note a significant increase in apathy in institutionalised individuals with DS aged 50 years or older ($n = 29$) compared with control groups ($n = 24$). Interestingly, individuals with DS aged 31 to 40 years had significantly lower apathy scores than controls. Although Thase and colleagues[40] did not formally diagnose dementia, they found significantly lower scores for orientation, digit span, visual memory, object naming and general knowledge in individuals with DS compared with controls.

Evenhuis[41] described the natural history of dementia in DS. She followed 17 middle-aged patients with DS until death. In total, 14 individuals had a clinical diagnosis of dementia and autopsy features of Alzheimer-like changes. The clinical pattern of deterioration was different in individuals with moderate ID compared with those with severe ID, although the numbers were small (9 *vs.* 5). In individuals with moderate ID and DS, early symptoms of dementia recognised by the staff included apathy, withdrawal, daytime sleepiness and loss of self-help skills.[41] Interestingly, memory disturbance was part of the early presentation in only three out of nine individuals. It was not until the second or third year that symptoms of remote memory loss, disorientation and apraxia (loss of ability to perform tasks despite intact motor and sensory functioning) were detectable. Also

by the third year the remaining six individuals with moderate ID showed recent memory loss.

Evenhuis[41] reported that, in contrast to individuals with both DS and moderate ID, adults with severe ID and DS showed apathy, loss of self-help skills, loss of gait and seizures during the first year of dementia. Evenhuis[41] could not demonstrate cognitive deterioration in individuals with severe ID. In support of Evenhuis' observation of increased seizures and dementia, a study published by Van Buggenhout and colleagues[42] found that 9 out of 18 individuals with dementia had seizures. Furthermore, Van Buggenhout's group believed that the onset of seizures was often one of the first signs of DAD if it occurred in older adults with DS.

Lai[29] also described a different pattern of deterioration depending upon whether the person with DS had higher functioning or more severe ID. Memory impairment, temporal disorientation and reduced verbal output were the initial findings in higher-functioning adults with DS. In contrast, those individuals with more severe ID became less interactive with others and this was the initial hallmark of dementia. The second phase showed a decline in activities of daily living, slowed gait and the emergence of seizures. Seizures usually developed within two years of the onset of dementia. In the final phase, individuals became bedridden and incontinent.[29]

Like Evenhuis,[41] Holland and colleagues[43] found that the early deterioration was more often in personality and behaviour than in memory. These researchers used a modified version of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)[44] to diagnose dementia. Holland and colleagues found that 10 out of 18 individuals (55%) showed apathy, while only 2 out of 18 (11%) experienced memory loss as the first change.[43] Loss of self-help skills occurred in only 3 out of 18 individuals (17%). The authors of the study believed that frontal lobe deficits were manifested early because of reduced cerebral capacity in individuals with DS.

In the general population, apathy is considered by some to be the most common behaviour resulting from AD.[45] The frontal subcortical circuitry appears to be involved. The study of apathy is plagued by imprecise definitions. Landes and colleagues[45] emphasise that some researchers have defined apathy as an absence of emotion or as emotional withdrawal. They note that others also include lowered initiative, reduced physical activities, indifference to activities, decreased responsiveness, poor persistence and fatigue. The distinction between apathy and depression will be discussed in the section on differential diagnosis.

In contrast to Evenhuis[41] and Holland,[43] Oliver and colleagues[46] focused mainly on cognitive change. They conducted a four-year prospective study of age-related cognitive change in adults with DS, which revealed that although neuropathological studies indicate a high risk for DAD in adults with DS, neuropsychological studies suggest a lower prevalence of dementia. In this study, cognitive deterioration in adults (n = 57) with DS was examined prospectively over a period of four years in order to establish the rates and profiles of cognitive deterioration. Assessments of domains of cognitive function that are known to change with the onset of dementia were employed. These included tests of learning, memory, orientation, agnosia, apraxia and aphasia, and the individual growth trajectory methodology was used to analyse change over time. Severe cognitive deterioration, such as acquired apraxia and agnosia, was evident in 28% of individuals

aged over 30 years, and a higher prevalence of these impairments was associated with older age. The rate of cognitive deterioration also increased with age and degree of pre-existing cognitive impairment. In addition, deterioration in memory, learning and orientation preceded the acquisition of aphasia, agnosia and apraxia, which suggests that the prevalence of cognitive impairments consistent with the presence of dementia is lower than that suggested by neuropathological studies. The pattern of acquisition of cognitive impairments in adults with DS is similar to that seen in individuals with DAD who do not have DS.

A study of neurological changes and emotions in adults with DS yielded significant results for individuals with pathological findings on magnetic resonance imaging (MRI) and neurological examination across three scales, namely depression, indifference and pragmatic language functioning.[47] Problems of poor pragmatic language functioning appeared later in the course of suspected DAD, but not at initial testing. In these individuals, the primary emotional change was a decline in social skills such as conversational style, literal understanding and verbal expression. These emotional levels were stable over time, regardless of the degree of cognitive decline. The emotional changes were associated with abnormal findings from MRI and neurological examination. These results, together with abnormalities in brain imaging and the presence of pathological reflexes, suggested that frontal lobe dysfunction was likely to be an early manifestation of AD in DS.[47]

Another brain-imaging approach to determining the natural history of dementia in DS is to measure brain areas and memory function in prodromal phases of DAD.[48] Krasuski and colleagues found that the volumes of the right and left amygdala, hippocampus and posterior parahippocampal gyrus were positively associated with age in adults with DS without dementia.[48] Furthermore, the amygdala and hippocampal volumes correlated with memory scores.

Differential diagnosis of cognitive and functional decline

A decline in functioning in an adult with DS does not automatically mean that DAD is present. Evenhuis[49] discussed false-positive scores on the DMR in 44 adults with DS. Nearly 30% of these 44 individuals had false-positive scores. Of the false-positive results that were related to physical causes, two were due to hearing loss, and one each was due to chronic tonsillitis, depression, arthrosis, visual loss and hypothyroidism. Other conditions to consider include Parkinsonism, cerebrovascular disease, folate deficiency, vitamin B_{12} deficiency and hypercalcaemia.[50]

Hearing loss is very common. Only 7% of 90 individuals with DS had normal hearing in one study.[42] In the subgroup aged 50 years or older, only 1 out of 30 individuals (3%) had normal hearing. Van Buggenhout and colleagues examined vision and found that almost half (45%) of those aged 50 to 59 years had moderate to severe visual loss. Visual problems were common in another review of elderly patients with DS. Van Allen and colleagues[51] reported that 13 out of 20 individuals (65%) had adult-onset cataracts. Overall, 75% of elderly people with DS had visual problems. Van Allen and colleagues emphasised that even something that most middle-aged people regard as routine, namely wearing bifocals, can be problematic for many individuals with DS.

Van Buggenhout and colleagues[42] tested for thyroid dysfunction and found that nearly half of their study subjects had abnormal thyroid-stimulating

hormone (TSH) levels. Most of the abnormalities were sub-clinical. The researchers found that 35% of individuals with DS aged over 50 years required treatment for hypothyroidism. Thyroid disorders in adults with DS will be discussed in detail in Chapter 7.

Burt and colleagues[52] emphasised that the extent of depressive symptoms associated with the onset of dementia in adults with DS is unclear. They studied 61 adults with DS, ranging in age from 20 to 60 years (average age 33.5 years). Their control group included 43 age-matched adults with intellectual disabilities but without DS. Burt and colleagues listed at least 15 symptoms that are common to both depression and dementia in individuals with DS. These included apathy/inactivity, loss of self-help skills, depression, urinary incontinence, irritability, slowing, being uncooperative/unmanageable, loss of housekeeping skills, greater dependency, loss of interest in surroundings, weight loss, emotional deterioration, destructive behaviour, hallucinations/delusions and sleep difficulties. They concluded that individuals with DS and depression are at increased risk of a decline in functioning. What the study could not determine was whether treatment of depression in older adults with DS reverses this functional decline.

Other differential conditions to consider are sleep apnoea and bereavement. Sleep apnoea is more common in adults with DS.[53] Folstein and Hurley[54] recommended that an evaluation of sleep apnoea should take place as part of the dementia work-up, especially if the person with DS is obese or snores loudly. Pary[55] described the case of Mr A, a 48-year-old man with DS who was referred to the clinic with probable dementia. Towards the end of the evaluation, the informants remarked that Mr A's mother had died nearly a year previously. Furthermore, Mr A had been unaware of his mother's death until several months after the funeral. Pary concluded that the functional decline disappeared following grief work, including Mr A visiting his mother's grave. Perhaps what was most remarkable about the vignette was that Mr A had severe ID and his carers were not aware that his mother's death could have much of an impact on him.

Perhaps one of the toughest differentials to untangle is that between depression and apathy associated with DAD. Landes and colleagues[45] have attempted to distinguish between the two. They list the symptoms of apathy as blunted emotional response, indifference, low social engagement, diminished initiation and poor persistence. The symptoms common to apathy and depression include diminished interest, psychomotor retardation, fatigue/hypersomnia and lack of insight. Landes and colleagues list the symptoms of depression as dysphoria, suicidal ideation, self-criticism, guilt feelings, pessimism and hopelessness. The sobering question for clinicians and researchers is 'How many adults with DS at their premorbid functioning could spontaneously voice suicidal thoughts, show self-criticism, or express guilt, pessimism or hopelessness?'

Overview of the clinical evaluation

One needs to critically examine adults with DS who present with functional decline, in order to avoid mistakenly assuming that all decline in dementia is due to DAD (as was done in the section on prevalence), and to take a cautious approach to the clinical work-up of dementia in DS. In individuals with DS, DAD is still a diagnosis of exclusion. Thus if a patient shows a functional decline and a disturbance of memory, one needs to rule out potential reversible causes before

assuming that the patient has dementia. Smith[53] has previously commented that 'neuropsychologic testing and radiologic imaging do not accurately diagnose dementia or reliably [distinguish] depression from dementia.' Although Smith[53] did not provide any data for his position, his view deserves some reflection. His opinion is based on years of experience as a family practitioner with a special interest in the health problems of adults with DS. Janicki and colleagues[56] offer a variation on Smith's view. They recommend repeated evaluations to increase confidence in the diagnosis (for specific diagnostic criteria the reader should consult their article). However, the Royal College of Psychiatrists in the UK cautions that repeated psychometric or behaviour skill assessments are insufficient by themselves to diagnose dementia.[50]

The goal of the clinical evaluation of DAD in individuals with DS has not changed since clinicians first pondered the aetiology of functional decline. The aim is still to rule out all potential reversible causes. After it has been shown that reversible causes are unlikely, one can (tentatively) conclude that the person has dementia, probably of the Alzheimer type. Pary[55] reviewed the clinical evaluation and emphasised that the first step is for the family or caregiver to recognise that there may be a deterioration in functioning. Theoretically an adult with DS could request the evaluation, although the authors are unaware of this ever happening. Often the impetus for an evaluation will be a loss of bathing or eating skills, loss of social or occupational skills or a personality change. Prasher and Chung[57] advise that individuals with more severe ID may show a greater age-related decline.

The cornerstone of the initial clinical evaluation is still a history from a reliable informant and a physical examination. Ideally the informant will have had daily contact with the person for years. However, in some clinical situations the informant may be any available member of staff, regardless of their knowledge about the patient. The evaluator should insist that the informant has known the person with DS for at least one year. This recommendation is based in part on a Royal College of Psychiatrists criterion[50] that requires at least six months of symptoms and a distinct change from premorbid functioning. Table 1.1 lists the areas on which to focus during the examination.

Unfortunately, there still is no laboratory test for diagnosing DAD. Measurement of plasma levels of Aβ1–42 is still confined to research centres and is not yet established as a marker for AD. Brain imaging is not diagnostic, although many lay people assume that brain imaging is part of the work-up for dementia. In the absence of lateralising signs on neurological examination, one could argue that the risks of sedation outweigh the potential benefits of MRI or computerised tomography (CT). An MRI study by Prasher and colleagues[58] was terminated because of poor patient compliance (i.e. remaining still in the MRI tube) and post-procedure complications due to sedation. Blood measurements should include thyroid function tests, complete metabolic panel (electrolytes, liver enzymes, calcium, creatinine and blood urea nitrogen), a complete blood count with platelets, folate and vitamin B_{12} levels.[55]

If unlimited time and resources are available, the test battery[22] outlined above merits consideration, although one could still not definitely conclude that a patient has DAD based on a single test battery. For most clinicians, then, serial tests using the DSDS[24] or DMR[23] questionnaire are a reasonable option. Some clinicians make serial videos (over a period of years) of simple commands and find this to be quite an effective way of demonstrating dementia.

Table 1.1 Examination in adults with DS, adapted from Smith[53]

System	*Possible findings*
Vital signs	Arrhythmias, obesity
Ears	Impacted cerumen, hearing loss
Eyes	Visual loss, cataracts, keratoconus
Mouth	Dental abscesses, periodontal disease
Neck	Enlarged lymph nodes, enlarged thyroid gland
Lungs/back	Pneumonia, tenderness over spine or kidneys
Heart	Murmurs, arrhythmias, mitral clicks
Abdomen	Masses, enlarged liver or spleen, hypotonic bowel sounds
Musculoskeletal	Gait disturbance or muscle atrophy (spinal cord compression, atlanto-axial subluxation)
Skin	Poorly healing sores (diabetes mellitus)
Genital	Testicular cancer
Neurological	Lateralising signs, pathological reflexes, Parkinsonian signs (increased rigidity; tremor)
Mental status examination	Crying or depressed mood, responding to internal stimuli, aphasia, apraxia, agnosia, impaired memory, disorientation, alterations of consciousness, psychomotor abnormalities, compulsive behaviour

Management of individuals with Down syndrome and Alzheimer's disease

Janicki and colleagues[56] and Wilkinson and Janicki[59] have provided guidelines for managing individuals with DS and DAD. They believe that it is important to review all medications and to eliminate any unnecessary drugs. Individuals with dementia are vulnerable to delirium, and two of the commonest causes are drug interactions and excessively high drug levels. Comorbid medical conditions, such as urinary tract infections or pneumonia, should be treated. Carers must recognise safety issues such as the potential for wandering, dressing inappropriately for the weather conditions, the potential for scalding because of inability to adjust the shower or bath temperature, or swallowing difficulty and aspiration or choking on food.

There have been preliminary reports of the use of anticholinesterase inhibitors in individuals with DS and DAD (for a recent review and further information, see reports by Prasher and colleagues[60–62]).

Conclusion

As society anticipates that most people with DS will live well beyond 50 years, DAD remains a potential complication. No longer is it expected that everyone over 60 years with DS will develop clinical features of DAD. The remaining

chapters of this book will review what is known about the biological correlates of AD and DS and what advances tomorrow's patients, families, caregivers and clinicians can expect.

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Amyloid beta and tau proteins in Alzheimer's disease and Down syndrome

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