Dementia in older adults with Intellectual Disabilities – epidemiology, presentation and diagnosis

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Abstract

Background: As life expectancy of people with intellectual disabilities (ID) extends into older age, dementia is an increasing cause of morbidity and mortality. **Specific Aim:** To update and summarize current knowledge on dementia in older adults with ID by conducting a comprehensive review of the published literature from 1997-2008 with a specific focus on: 1. epidemiology of dementia in ID in general as well as in specific genetic syndromes 2. presentation and 3. diagnosistic criteria for dementia. **Method:** Combination of searches in electronic databases Medline, EMBASE, Psych Info for original research papers in English, Dutch or German.

Findings: Varied methodologies and inherent challenges in diagnosis yield a wide range of reported prevalence rates of dementia. Rates of dementia in the population with intellectual disability not due to Down syndrome (DS) are comparable to or higher than the general population. Alzheimer's disease in DS is early in onset and the prevalence increases from under 10% in the 40s to more than 30% in the 50s, with varying prevalence reported for those 60 and older. Incidence rates increase with age. Few studies of dementia in other genetic syndromes were identified. Presentation differs in the ID population compared to the general population; those with DS present with prominent behavioral changes believed to be due to frontal lobe deficits. **Discussion:** Dementia is an important disorder of older age in people with intellectual disabilities in general as well as people with DS specifically. The challenge for the next ten years is to conduct large-scale collaborative studies of high quality to further our knowledge on the epidemiology and clinical presentation of dementia in this population.

Introduction

Life expectancy of individuals with intellectual disabilities (ID) has significantly increased over the past fifty years and this trend will continue into the future. With increased life expectancy comes age-related illness, including dementia. Dementia is a growing source of morbidity and mortality in this population. A previous review has suggested that the epidemiological pattern i.e. the incidence and prevalence of dementia (particularly Alzheimer's Disease) among the ID population may differ from that in the general population, at least in specific subgroups such as Down Syndrome (DS) (Zigman, Schupf, Haveman, & Silverman, 1997). There are also several reasons why dementia may present atypically in the ID population. The perception of decline and the way it manifests will depend on the premorbid level of ID and pattern of cognitive abilities, and the environmental demands placed on the person. Co-morbid conditions such as epilepsy will further complicate the picture, and aging itself may contribute to some degree of decline. The application of standard diagnostic criteria, which are based on the development of specific cognitive deficits in adults without ID, therefore requires careful consideration (Aylward, Burt, Thorpe, & Lai, 1997; Janicki, Heller, Seltzer, & Hogg, 1996; Thorpe, Davidson, & Janicki, 2001).

The study of 'dementia' in relation to people with ID is fraught with other anomalies. We now know that almost all adults with Down Syndrome have the microscopic plaques and tangles associated with a diagnosis of Alzheimer's Disease (AD) in their thirties, but many never develop the signs or symptoms of dementia, and that older males with fragile X pre-mutation may develop Fragile X Ataxia Syndrome, characterized by cognitive decline and mobility problems.

In the lead up to the 13th World Congress of IASSID, the Special Interest Research Group on Ageing in Intellectual Disability sought to review the state of recent literature on aspects of ageing. This paper reports on the epidemiology and presentation of dementia in people with ID – there is an accompanying paper on dementia care-giving issues, and others focus on physical health and ageing.

Aims of this review

We aimed to update and summarize current knowledge on dementia in older adults with ID through a comprehensive review of the published literature over the past decade, i.e. from 1997 – 2008, addressing:

1. epidemiology, with a specific focus on genetic syndromes and their association with dementia;
2. presentation and symptoms; and
3. diagnostic criteria for dementia in this population

Method

Literature search

We undertook computerized searches of Medline, EMBASE, and Psychinfo using the exploded MESH term “mental retardation”, as well as title and abstract searches for equivalent terms (mental retardation or mental handicap or intellectual disabilit* or learning disabilit*). We also used the MESH term “Down syndrome”, as well as title and abstract searches for equivalent terms (Down's syndrome or Down syndrome). These were combined (using the AND function) with the exploded MESH term “dementia” as well as title and abstract searches for dementia and equivalent terms (Alzheimer's disease or vascular dementia or Parkinson's dementia or Lewy body dementia or fronto-temporal dementia or front* degeneration). The search was limited to publication dates from 1997, and was undertaken at the end of April 2008. This strategy delivered several thousand abstracts.

Enhanced search for ID syndromes and dementia

Since the general search term “mental retardation” and its equivalents may not include all ID syndromes, and because we had a particular interest in dementia in specific syndromes, additional searches were performed for known ID syndromes, which were combined with the term “dementia” in the title or abstract. Finally, we searched for data on mortality in specific syndromes (without date limiters), in order to find out whether individuals with a specific syndrome may reach adulthood and therefore be at risk of developing dementia.

Selection of papers

For this review, we selected all papers in English, Dutch or German reporting original research on epidemiology and presentation of dementia in ID. We also included reviews published since 2003. We excluded case reports (unless it described specific syndromes) as well as basic sciences research unless it concerned humans with dementia and reported clinical associations. The reviewers added relevant publications from their personal collections if not already included. All the research papers included in this review are summarized in tables 1, 2 and 3, but where relevant, other papers were quoted in the text.

Epidemiology of dementia in adults with ID

Studies concerned with the prevalence or incidence of dementia in older adults with ID are summarized in tables 1 and 2. We have not included studies that have focused on longitudinal change without making a diagnosis of dementia, e.g. (Carr, 2003; Oliver, Crayton, Holland, Hall, & Bradbury, 1998; Zigman, Schupf, Urv, Zigman, & Silverman, 2002) which are summarized elsewhere (Carr, 2005). Since prior research indicates that the risk of dementia, and

in particular AD, is much higher among the population with DS, we classified the papers into one of the following three categories:

1) studies which did not distinguish between those with and without DS
2) studies which focused on the population with DS;
3) studies which focused on the ID population who do not have Down syndrome (non-DS ID).

The reviewed studies varied considerably in the population studied, in the design of the study, and in the size of the population studied. Some included only institutionalized participants, but the majority were population-based studies, which involved individuals living in community settings as well as in institutions (see tables 1 & 2). Studies that included only institutionalized samples may have been biased as people living in long-term facilities are usually more severely disabled. The ascertainment of cases differed between studies. Studies that made direct assessment of participants and included information given by caregivers as well as medical records are likely to have the most reliable estimates of prevalence and incidence. Studies that relied on third party report of diagnoses or symptoms rather than on assessments with individual participants may have under-estimated dementia rates. In most of the studies we identified, well-accepted criteria for the diagnosis of dementia in adult population with ID were used, though those criteria differed between studies. Different criteria may result in diagnosing different cases. A few prevalence studies were able to confirm diagnoses with follow-up assessments, e.g. (Zigman, et al., 2004), but most were entirely cross-sectional. Given the methodological differences among the studies conducted, it is difficult to undertake direct comparisons of findings.

With regard to prevalence and incidence studies of dementia in adults with ID, we included all studies we found, but used three basic criteria to identify studies which were of sufficient epidemiological standard. Firstly, we rated whether samples were representative of the ID or DS population. A study was deemed to be representative if it made use of unbiased sampling methods, and if it was based on a population that is representative of all older adults with ID or DS. However, for practical reasons the vast majority of epidemiological surveys in the ID population make use of populations identified by services. We rated studies to be sufficiently representative if they included both community and institutional service defined populations. Secondly, studies had to have undertaken standardised individual assessments with participants to identify potential dementia cases, and thirdly, should have used standardised diagnostic criteria to diagnose cases. The studies rated to meet these requirements are marked in tables 1 and 2, and the main findings of this section were based on these studies. We acknowledged the methodological differences when comparing the estimated rates of dementia across different studies.

We did not rate the studies of dementia in rare syndromes according to the above criteria, as these populations are very small and there were very few relevant studies . These studies are summarised in table (3).

The majority of studies were conducted in Europe (the Netherlands, Ireland and the UK) and the US. There was only one published study from Asia, and none from South America, Eastern Europe, Africa or Australia and New Zeeland. The variation in the size of the study samples as well as the sample selection methods may explain some of the diversity observed in the findings.

Dementia Prevalence

Dementia prevalence among population with ID

A few studies have reported estimates of population-based prevalence of dementia in an overall population of persons with ID. Janicki and Dalton (2000) conducted the most recent study in New York State, USA, based on a postal survey of known dementia cases amongst adults using ID services – individual assessments were not undertaken. The overall prevalence rate of 6.1% in those aged 60 and older was comparable to that in the general population (Ferri et al, 2005). Among adults with Down syndrome, the rates were higher - 22% for those aged 40+ and 56% for those aged 60 and older. The mean age of dementia onset among individuals with Down syndrome was 52.8 years. For individuals with other types of ID it was 67.2 years (Janicki & Dalton, 2000).

Dementia prevalence among the population with Down syndrome

The majority of the prevalence studies we found focused on adults with DS (Table 1). Several of these studies were representative surveys, which included adults from community as well as institutional settings. Often, the sampling frame was the entire DS population of an area or district (Coppus, et al., 2006; Holland, Hon, Huppert, Stevens, & Watson, 1998). These studies confirmed that dementia is common in older adults with DS, and that the prevalence increases sharply from the age of 40 until the age 60. For example, in the UK, using CAMDEX criteria for Alzheimer's disease prevalence rates increased from 3.4% to 10.3% to 40% among 30-39, 40-49 and 50-59 age groups, respectively (Holland, et al., 1998). In Ireland, using modified DSM IV criteria to diagnose cases, age-specific prevalence rates were as follows: 1.4% for those under age 40; 5.7% for those 40-49 years of age; 30.4% for those 50-59 years of age (Tyrrell, et al., 2001). The largest study of dementia in the DS population to date was in the Netherlands, based on the total population of one province and included 506 participants with DS aged 45 years and older (Coppus, et al., 2006). Up to the age of 60, the prevalence of dementia doubled with each 5-year interval. Up to the age of 49, the prevalence was 9%; between the ages of 50 and 54,

17.7%; between 55 and 59, it was estimated at 32.1%.

There was considerable variation between studies for the prevalence of dementia beyond the age of 60. Tyrrell and associates (2001) described a rate of 41.7% among those aged 60 and over, and 50% among those aged 70 or older; while Coppus et al. (2006) described a decrease in prevalence to 25.6% beyond age 60 which was thought to be due to either a decline in incidence, or an increase in mortality rate in those with dementia (Coppus, et al., 2006; Tyrrell, et al., 2001). One other study, based on an institutional sample, described a rate of 100% in adults with DS aged 65 and older (Visser, Aldenkamp, Van Huffelen, & Kuilman, 1997).

No gender differences have been found for dementia rates in older adults with DS (Coppus, et al., 2006; Tyrrell, et al., 2001), but the average age of menopause of women with DS was younger than in the general population, and the age at onset of dementia was correlated with the age of menopause for those who developed dementia (Cosgrave, Tyrrell, McCarron, Gill, & Lawlor, 1999).

Dementia prevalence among population with non-DS ID

Only a few studies focused on the prevalence and/or incidence among adults with ID who do not have Down syndrome. Two studies have been undertaken in the UK (table 1). Cooper (1997) conducted a population-based study of 134 elderly people with ID over the age of 65 (five of whom had DS). Dementia was diagnosed in 21.6% which was substantially higher than that found in the general population (Cooper, 1997). Strydom and associates (2007) established a sample of 222 urban adults with ID aged 60 and older. Dementia cases were identified after a two-phased process – a screening phase, followed by comprehensive assessment of screen positives. Using ICD-10, DSM-IV, DC-LD and dementia subtype criteria, the overall dementia prevalence was 13.1% (95% CI 8.9-18.2) among those aged 60 and older, and 18.3% (95% CI 12.3-25.7) among those aged 65 and older. Alzheimer's disease was the most common type, and had a prevalence rate of 12% (7.1 – 18.5%) among those aged 65 and older, three times greater than general population rates. Lewy body and fronto-temporal dementias were, interestingly, more common than vascular dementia.

Zigman et al. (2004) conducted a longitudinal study of 126 adults with ID without DS over the age of 65 in the USA. The sample consisted of a random selection of registered users of ID services, supplemented with a convenience sample and the authors employed comprehensive assessments repeated at 18 month intervals. They identified 10 cases with possible, definite or complicated AD (prevalence rate 9% for those aged 65 and older; 12% for those 75 years and older). These rates were within the range of rates for older adults without ID in the USA (Zigman, et al., 2004).

The difference in prevalence rates between the UK and US may be explained by the methodology. Although the UK estimates were based on samples representative of service users,

the diagnoses were based on a single evaluation rather than on longitudinal assessments, and this may have over-estimated dementia. The American study may have under-estimated dementia by not including all dementia subtypes, by using more restrictive criteria, or by being less representative than the UK studies by including a convenience sample. However, like-for-like estimates for AD prevalence according to ICD 10 criteria were similar in the UK and USA (Strydom, Livingston, King, & Hassiotis, 2007; Zigman, et al., 2004).

Dementia Incidence

In dementia incidence studies, it is important to consider the age distribution of the cohort, the rigor with which dementia cases at entry are excluded, the length of follow-up and the diagnostic methods and criteria used. We have summarised all the incidence studies found in the literature search in table 2..

Dementia Incidence among the population with Down syndrome

The majority of reviewed studies were of cohorts of individuals with DS, summarised in table (2). For example, Visser et al. (1997) described the dementia incidence over a 6 year period among 307 institutionalized participants in the Netherlands. Among those aged 40 years and above at entry, the incidence rate was 36%. Incidence increased steadily with increasing age, and did not appear to taper off in those aged 60 and older (Coppus, et al., 2006). Decreased prevalence in adults with DS aged 60 and older noted in this study therefore appeared to be due to an increase in mortality of those with dementia, which was more than twice that of those without dementia.

The survival period from onset of dementia at age 55 until death was 3.5 years (SD 2.2) for incident cases in an institutional sample of more severely disabled adults (Margallo-Lana, et al., 2007), while the mean age at death was 59.3 (SD 10.2) years. In this study, the incidence rate of dementia was 25% over 15 years, which seems to be low compared to other studies, possibly due to the difficulties in diagnosing dementia in those with profound ID. However, the study was unusual in that neuropathological findings were available for many of those who had died and among those with a diagnosis of dementia, it was associated with the density of tangles, but not plaques.

Dementia incidence among population with non-DS ID

Zigman and colleagues (2004) also reported incidence rates from their longitudinal study of adults with ID without Down syndrome over the age of 65, although the sample size was reduced in each subsequent wave of data collection. The incidence rate for AD was 8 cases in a cohort of an estimated 100 participants (aged 65 – 84) over 3 years, with a cumulative incidence rate of 0.31 (Zigman, et al., 2004).

Dementia in specific ID syndromes other than DS

Although we have found several studies describing Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), a disorder characterized by progressive action tremor, ataxia and dementia that occurs in premutation carriers of the FMR1 (fragile X mental retardation 1) gene (Hagerman & Hagerman, 2004), we did not include it in this review because FXTAS itself is not associated with ID. Little attention has been paid to the risk of dementia in other specific ID syndromes. We have summarized in table 3 the common syndromes which have been associated with development to adulthood. Although these adults often have reduced life expectancy, many reach middle age and could therefore develop dementia.

Several syndromes have "dementia" as a common characteristic – these include Cockayne syndrome, Rett syndrome and Sanfilippo syndrome. Cockayne syndrome (Progeria-Like-Syndrome), a rare autosomal recessive disorder, is characterized by premature ageing, including dementia (Rapin, et al., 2006).

Rett syndrome

Rett syndrome is a childhood neurodevelopmental disorder which manifests particular symptoms at certain ages. The general Rett profile is that of a slow deterioration of gross motor performance over the years in contrast with a relatively preserved cognitive ability to communicate, mainly with the eyes. The condition stabilizes to some extent after childhood, but many of the women with this disorder now live into old age with progressive neuromuscular problems (Hagberg, 2005; Halbach, et al., 2008). Occurring almost exclusively in girls, it is believed to be due to a mutation in the MECP2 gene on chromosome X, a transcriptional repressor presumed to be essential for neuronal function of the maturing brain (Van den Veyver & Zoghbi, 2002). Rett syndrome was initially described as being a progressive syndrome of autism, dementia, ataxia and loss of purposeful hand use in girls (Hagberg, Aicardi, Dias, & Ramos, 1983). There is now doubt about the progressive nature of the disorder and whether the term "dementia" should be used to describe the deterioration. Because of various functional, physical, anatomic and chemical features, it has been hypothesized that Rett syndrome could be a disorder of development (Einspieler, Kerr, & Prechtl, 2005).

Sanfilippo syndrome

The Sanfilippo syndrome, or mucopolysaccharidosis III (MPS III), is a lysosomal storage disease due to impaired degradation of heparan sulfate and includes 4 types, each due to the deficiency of a different enzyme: heparan N-sulfatase (type A); alpha-N-acetylglucosaminidase (type B); acetyl CoA:alpha-glucosaminide acetyltransferase (type C); and N-acetylglucosamine 6-sulfatase (type D) (Yogalingam & Hopwood, 2001). The Sanfilippo syndrome is characterized by severe central nervous system degeneration, but only mild somatic disease. The onset of clinical

features usually occurs between 2 and 6 years; severe neurological degeneration occurs in most people between 6 and 10 years of age, and death occurs typically during the second or third decade of life. Type A has been reported to be the most severe, with earlier onset and rapid progression of symptoms and shorter survival; in type B, people survive into mid-life. A Dutch study showed that 18/20 of adults (aged 20-76 years) with Sanfilippo syndrome had dementia (Moog, et al., 2007). Another study, which included some of the same individuals as the previous study, showed that 17/29 of individuals (aged 7-72 years) had dementia (Skandar, Schoonbrood-Lenssen, Van den Akker, & Maaskant, 2005).

Other syndromes

Although we did not find any papers describing dementia cases in Williams syndrome (associated with a microdeletion of the long arm of chromosome 7), a group of researchers followed a number of adults with detailed psychometric assessments, and found the syndrome to be associated with precocious aging and loss of some cognitive abilities, specifically explicit memory functions (Krinsky-McHale, Kittler, Brown, Jenkins, & Devenny, 2005). However, none were diagnosed with dementia. Lastly, a study on Prader-Willi syndrome (in most cases due to a deletion on chromosome 15) found no dementia cases in a cohort of 74 individuals aged 18-63 years (Sinnema, Maaskant, Van Schrojenstein Lantman-de Valk, Schrander-Stumpel, & Curfs, 2008).

Table (1): Age-related Prevalence of Dementia in Intellectual Disability (ID) (DS and non-DS)

Authors (year)	Study Design	Location	Residence	Sample	Dementia Criteria	Age	Overall Prevalence (%)	Age-specific Prevalence (%)
Overall ID population								
Janicki & Dalton, 2000	Cross-sectional	New York State, US	Institution and Community	Overall ID Dementia cases = 794 DS dementia cases = 268	Postal survey of all ID services in one US state; not individually assessed; did not use specific diagnostic criteria	40+ 60+ 80+ 40+ 60+		3.0 6.1 12.1 22.1 56.4
Van Schrojenstein Lantman De Valk, et al., 1997	Longitudinal	The Netherlands	Institution and community	overall ID n = 1020 DS n = 243 Non-DS ID =	Questionnaires to General Practitioners of one Dutch province; not individually assessed; criteria used not stated	All ages 0-19 20-29 30-39 40-49 50-59 60-69 >70 0-19 20-29 30-39 40-49 50-59 ≥60 All ages	3.8 16.9 2.0	 1.0 - 0.8 5.1 5.4 6.2 17.6 - - - 22.2 45.7 72.7

				849		0-19 20-29 30-39 40-49 50-59 ≥60		1.3 - 1.1 - 1.7 5.9
Age-related Prevalence of Dementia in Down's Syndrome (DS)								
Coppus, et al., 2006	**Longitudinal study**	**The Netherlands**	**Community and Institution**	**506**	**All providers in 4 regions; Possible cases identified by informants, then individually assessed; diagnosed by ICD-10**	**45+ 45-49 50-54 55-59 60+**	**16.8 (16-23)**	**- 8.9 (95% CI 5-12) 17.7 (95% CI 12-23) 32.1 (95% CI 22-42) 25.6 (95% CI 12-40)**
Tyrrell, et al., 2001	**Cross-sectional**	**Ireland**	**Community and Institution**	**285**	**All DS users of selected providers of ID care across Ireland; individually assessed; diagnosed by DSM IV**	**35+ 35-40 40-49 50-59 60+ 70+**	**13.3**	** 1.4 5.7 30.4 41.7 50.0**
Van Buggenhout, et al., 1999	Cross-sectional	The Netherlands	Residents of one large Institution	96	Institutional sample; individually assessed; criteria not stated	50+	42.4	
Holland, et al., 1998	**Cross-sectional**	**UK**	**Community and Institution**	**75**	**All providers of one region; Individually assessed; . ICD 10; DSM IV, CAMDEX-AD, DLB and FTD criteria**	**30+ 30-39 40-49 50-59 30+**	**24.0 (All dementias) 13.3 (CAMDEX AD)**	** 20.7 20.7 40.0**

						30-39 **40-49** **50-59**		**3.4** **10.3** **40.0**
Sekijima, et al., 1998	Longitudinal assessment (1 year)	Japan	Institution	106	Institutions in one prefecture; Individually assessed, including CT scans; Criteria not specified	30+ 30-39 40-49 50+	15.1	 0.0 16.0 41.0
Visser, et al., 1997	Longitudinal	The Netherlands	Institution	307	Institutional sample; Individually assessed including EEGs; criteria not specified	All ages <39 40-49 50-59 60-69 >70	18%	 0.0 11.0 66.0 77.0 100.0
Age-related Prevalence of Dementia in non-DS ID								
Cooper, 1997	**Cross-sectional**	**UK**	**Community and Institution**	**134**	**Service user sample with no outreach; individually assessed; ICD-10 criteria**	**65+** **65-74** **75-84** **85-94**	**21.6**	**-** **15.6** **23.5** **70.0**
Zigman, et al., 2004	**Longitudinal**	**New York State, USA**	**Community And Institution**	**126**	**Random sample from state wide service register plus convenience sample. Individually assessed. DSM-IV AD criteria** **possible/definite AD or "uncertain with complications"**	**65+** **75+**		**9.0 (95% CI 4.2-16.4)** **12.1 (95% CI 5.0-23.3)**
Strydom, et	**Cross-**	**UK**	**Community**	**222**	**All adults receiving**			

al., 2007	**sectional**		**(urban) And institution**		**care in 5 London boroughs; Potential cases identified through screen then individually assessed ICD-10, DSM-IV, or DC-LD** **Any dementia** **AD on any criteria** **VaD on any criteria** **DLB on any criteria** **FTD on any criteria**	**60+** **65+** **65+** **65+** **65+** **65+**	**13.1** **18.3**	 **12.0 (95% CI 7.1-18.5)** **3.5 (95% CI 1.2-8.0)** **7.7 (95% CI 3.9-13.4)** **4.2 (95% CI 1.6-9.0)**

Studies that were rated to be of high epidemiological standard are marked in **bold** (See text).

Table (2): Incidence of dementia in ID

Authors (year)	Study Design	Location	Residence	Sample	Dementia Criteria	Age	Follow-up (Yrs)	# of Incident Cases	Incidence
Overall ID population									
Van Schrojenstein Lantman-de Valk et al. 1997	Longitudinal	The Netherlands	Institution and community homes	1041 ID	Questionnaires to General Practitioners; no assessments completed with participants; criteria used not known	All ages	3		% 2.7
				214 DS		30-39 40-49 50-59 ≥60			0.5 5.6 2.9 5.7
				827 non-DS ID,		30-39 40-49 50-59 ≥60			0.0 24.0 27.6 80.0
						30-39 40-49 50-59 ≥60			0.6 0.0 1.5 5.1

Incidence of dementia in Down's Syndrome									
Margallo-Lana, et al., 2007	Longitudinal	UK	Institution	92	Institutional sample; individually assessed; ICD10 criteria Neuropathology	38 (Median age at start)	15 years	18	25% over 15 years
Coppus et al. 2006	**Longitudinal**	**The Netherlands**	**Institution And Community**	**506**	**All providers of 4 regions; Possible cases identified by informants, then individually assessed; diagnosed by ICD-10**	**<50 50-54 55-59 ≥60**	**Mean 3.3 years**	**18 14 8 9**	**Per 100 person years 2.5 2.8 4.9 13.3**
Holland, Hon, Huppert, & Stevens, 2000	**Longitudinal**	**UK**	**Community And Institution**	**68**	**All providers of one region; individually assessed; ICD 10; DSM IV, CAMDEX-AD, DLB and FTD criteria**	**30+ 30-39 40-49 50-59**	**18 months**	**13 6 5 2**	**% 24.5 26.1 26.3 22.2**
Incidence of dementia in non-DS ID									
Evenhuis, (1997)	Retrospective Follow-up study	The Netherlands	Residents of one large Institution	144	Institutional sample; Individually assessed DSM-III-R	60+ 60-69 70-79 ≥80	11	 1 5 3	 % 1.6 (0.0-4.7) 19.1 (2.4-35.8) 29.1 (0.0-62.1)
Zigman et al. (2004)	**Longitudinal**	**New York State, USA**	**Community And Institution**	**100 (approx)**	**See above; DSM-IV (AD only) possible/ definite dementia or**	**65-84**	**3**	**8**	**cumulative incidence 0.31**

					“uncertain with complications”				

Studies that were rated to be of high epidemiological standard are marked in **bold** (See text).

Table 3. Specific syndromes: life expectancy, and dementia.

Syndrome	Cause	Life Expectancy (LE)	Dementia
Angelman	Most: deletion chromosome 15	Reaching adulthood; Reduced LE (<10-15 years) (Angelman-Syndrome-Foundation; Williams, 2008)	N=1 (case-study) (Bjerre, Fagher, Ryding, & Rosen, 1984) Regional cerebral blood flow studies showed reduced cerebral circulation compatible with organic dementia
Coffin Lowry	Most: mutation X-chromosome	Reaching adulthood, Reduced LE (Hunter, 2002)	-
Cornelia de Lange	Most: mutation chromosome 5	Reaching adulthood; Reduced LE (Begeman & Duggan, 1976; The-Cornelia-de-Lange-Syndrome-Association, 2008)	-
Cri du Chat	Deletion chromosome 5	Reaching adulthood; Reduced LE (Mainardi, et al., 2006)	-
Fragile X	Mutation X-chromosome	Reaching adulthood; Reduced LE (-10 y) (Partington, Robinson, Laing, & Turner, 1992)	-
Kabuki	Unknown	Reaching adulthood; Normal LE (?) (Kabuki-Syndrome-Network, 2008)	-
Klinefelter	Extra X-chromosome	Slightly reduced LE (2 y) (Bojesen, Juul, Birkebaek, & Gravholt, 2004; Swerdlow, Higgins, Schoemaker, Wright, & Jacobs, 2005)	-
Laurence Moon Bardet Biedl	Most: mutation chromosome 11	Reaching adulthood; Reduced LE (Riise, 1996)	-
Prader Willi	Most deletion chromosome 15	Reported sudden deaths; Reaching adulthood; Reduced LE (?) (Einfeld, et al., 2006)	0/74 (Sinnema, et al., 2008), based on parental report of dementia symptoms
Rett	Mutation *X*-	Reported sudden deaths; Reaching adulthood (Guideri &	See text

	chromosome	Acampa, 2005; Laurvick, et al., 2006)	
Rubinstein Taybi	Most: mutation chromosome 16	Reaching adulthood; Reduced LE (Mijuskovic, Karadaglic, & Stojanov, 2006)	-
Sanfilippo	A: mutation chr 17 B: mutation chr 17 C: mutation chr 8 D: mutation chr 12	Reaching adulthood; Reduced LE (see text)	18/20 (Moog, et al., 2007) based on review of medical records 17/29 (Skandar, et al., 2005) based on questionnaires to medical specialists
Sotos	Mutation chromosome 5	Expected Normal LE (National Institute of Neurological-Disorders and Stroke, 2007)	-
Velocardiofacial syndrome	Deletion chromosome 22	Reaching adulthood	N=1, case- study (Evers, Vermaak, Engelen, & Curfs, 2006) based on clinical assessment and DSM-IV criteria
Williams	Deletion chromosome 7	Reported sudden deaths but reaching adulthood (Bird, et al., 1996; Wessel, et al., 2004)	See text
Wolf-Hirschhorn	Deletion chromosome 4	Reaching adulthood; Reduced LE (Shannon, Maltby, Rigby, & Quarrell, 2001)	-

Presentation of dementia in adults with ID

A discussion on the presentation of dementia in ID is complicated by several issues. The first is that studies of dementia in this population rarely make a distinction between dementia subtypes. Secondly, dementia presentation may differ between people according to the severity of pre-existing ID. Lastly, it is important to distinguish the presentation of dementia in subgroups such as those with DS, because their unique cognitive profile and biological characteristics may be influential (Teipel & Hampel, 2006). We have therefore focused on aspects of dementia presentation specific to adults with DS separately from other adults with ID.

We have included all the studies that met our initial selection criteria, but have not rated the studies according to methodological quality because researchers have used a broad range of methods. Table 4 lists all the studies we found.

Dementia symptoms in adults with DS

Table 4 includes studies that have examined the presentation of dementia by observing the development of symptoms over time (longitudinal studies), or by making comparisons between those with and without dementia (cross-sectional studies).

Trigger symptoms in people with DS

Recent studies have continued the work of earlier authors e.g. Evenhuis, (1990) to describe the “trigger” symptoms associated with diagnosis of dementia in DS. Common symptoms included memory loss and deterioration in speech, personality and behavioral changes, disorientation, and functional deterioration (Cosgrave, Tyrrell, McCarron, Gill, & Lawlor, 2000; Visser, et al., 1997). Up to half of the cases presented with neurological symptoms, such as seizures and incontinence which are usually signs of advanced disease, suggesting that dementia presents atypically in DS, or reflecting the diagnostic difficulties, especially in those with more severe ID. Deb et al. (2007) made a qualitative summary of caregivers’ reports of early symptoms. Forgetfulness and confusion were the most prominent symptoms but many 'frontal lobe'-related symptoms that usually manifest later in the course of dementia among the general population, were also common. These included slowness in activities and speech, loss of interest and withdrawal, and the emergence of emotional and behavior problems (Deb, Hare, & Prior, 2007).

Memory and other cognitive changes in people with DS

Several researchers have used sequential cognitive assessments to track the changes that occur with the development of dementia in adults with DS. Similar to AD in the general population, memory change appears to be an early symptom in DS and is present before the

person meets the full clinical criteria for dementia (Devenny, Krinsky-Mchale, Sersen, & Silverman, 2000; Devenny, Zimmerli, Kittler, & Krinsky-Mchale, 2002; Krinsky-Mchale, Devenny, & Silverman, 2002). Cognitive decline associated with early and middle stage dementia involved progressively more areas of cognitive functioning, starting with complex cognitive functions, followed by visual organization as well as verbal memory before affecting semantic and short-term memory (Devenny, et al., 2000).

These results are in keeping with other studies that have demonstrated that the diagnosis of dementia was associated with early deficits in both memory and executive functioning tasks (Ball, Holland, Treppner, Watson, & Huppert, 2008; Kittler, Krinsky-McHale, & Devenny, 2006) though it is not clear whether these develop together or sequentially. Dyspraxia occurs at a later stage (Crayton, Oliver, Holland, Bradbury, & Hall, 1998; Dalton, Mehta, Fedor, & Patti, 1999).

Functional, personality or behavioral changes

Many studies have sought caregiver reports on the presentation of dementia, often out of necessity, given the ability profile of many adults with DS. Cosgrave et al. (2000) described decline in activities of daily living (ADL) as a trigger symptom in 48% of their dementia cases, which progressed from deterioration in personal hygiene to housekeeping skills and spatial orientation (Cosgrave, et al., 2000; Prasher, Chung, & Haque, 1998). These continued to deteriorate with progression until it floored, with dressing, spatial orientation and eating being the last to floor.

Several studies have confirmed earlier reports of prominent personality and behavioral change in those with DS and dementia (Lai & Williams, 1989) and they appear to be a harbinger of the disorder in adults with DS (Ball, et al., 2006; Holland, et al., 2000; Nelson, Orme, Osann, & Lott, 2001). Ball et al. (2006) made the interesting observation that many older adults with DS meet criteria for dementia of frontal type which they described as a preclinical stage of AD, before they progress to meeting the criteria for AD. They also showed that personality change is associated with executive dysfunction (Ball, et al., 2006; Ball, et al., 2008). Individuals with dementia displayed an increased number of and more severe maladaptive behaviors (Prasher, et al., 1998; Urv, Zigman, & Silverman, 2008) that can be divided into two types – behavioural excesses such as irritability, aggression or self-abusive behaviour, or behavioural deficits such as general slowness, apathy or loss of interest, and decreased social engagement (Cosgrave, et al., 1999; Deb, Hare, & Prior, 2007; Huxley, Van Schaik, & Witts, 2005; Urv, et al., 2008). Behavioral excesses rather than deficits triggered referral for dementia assessment (Adams, et al., 2008). This has important implications - many older adults with DS may have dementia symptoms but do not get assessed until their behavior becomes troublesome to their caregivers.

One study compared the behavioral and emotional changes associated with AD between 30 individuals with DS and AD, and 30 individuals with AD from the general population (Temple &

Konstantareas, 2005). The DS group experienced fewer delusions and problem behaviors overall but was more physically active compared to the AD-only individuals.

Neurological and other physical findings

Epilepsy and myoclonus is often associated with dementia in DS, especially in those with severe ID (Cosgrave, et al., 2000; Margallo-Lana, et al., 2007; Tyrrell, et al., 2001; Visser, et al., 1997). Late onset myoclonic epilepsy in DS (LOMEDS) is characterized by myoclonic jerks on waking, generalized tonic-clonic seizures, and generalized spike and wave on EEG; an interesting observation is that AD and progressive myoclonic epilepsy are both linked to chromosome 21 (Menendez, 2005). Pathological reflexes such as grasping and sucking reflexes and concomitant atrophy on neuro-imaging was shown to be significantly related to behavioral changes associated with frontal lobe problems (Nelson, et al., 2001). This is in keeping with the hypothesis that frontal dysfunction is a prominent feature of dementia in DS. Other common neurological symptoms have included rigidity and postural abnormalities (Margallo-Lana, et al., 2007).

Those with dementia have more health co-morbidities than those without (McCarron, et al., 2005) especially lung disease, gastro-intestinal disorders, visual and hearing impairments; and often lose weight (Prasher, Metseagharun, & Haque, 2004). This might be due to dysphagia or other factors such as loss of appetite, difficulty with feeding, malabsorption, and concomitant medical conditions (Lazenby, 2008). Some may require tube feeding as their condition deteriorates (McCarron, et al., 2005).

End-stage symptoms

Cosgrave et al. (2000) and Visser et al. (1997) have described 14 and 41 subjects respectively with end stage dementia. All were unresponsive to their environment and lost the ability to speak. They were totally dependent and unable to walk, all were incontinent, and almost all had seizures and many had Parkinsonian features.

Dementia presentation in older adults with non-DS ID

In a UK study of 26 dementia cases caregivers descriptions at first presentation of symptoms included a general deterioration in functioning (50%), followed by behavioral or emotional change (15%). Deterioration in memory and other cognitive functions were less prominent in the early stages of the disorder (Strydom, et al., 2007). Other signs included signs of depression such as lack of energy, low mood, and disturbed sleep; persecutory delusions and auditory hallucinations, or delirium; while late stage symptoms such as urinary incontinence, difficulty in walking and fecal incontinence were surprisingly common (Cooper & Prasher, 1998; Evenhuis, 1997). Compared to those with DS and dementia, aggression occurred with greater

frequency in those with non-DS ID, but the DS cases had a higher prevalence of other behavioral changes (Cooper & Prasher, 1998).

Table 4: Studies of the presentation of dementia in DS since 1997

Authors	Number & age of participants	Type of study	Presentation under study	Main findings
Visser, et al., 1997	N = 307, age 10 – 72; 56 had dementia	Longitudinal	Onset and progression of symptoms	Initial onset was non-specific (loss of interest, motivation etc.). See text for end stage symptoms
Prasher, et al., 1998	N = 128, age 16 – 72; 17 had dementia	Longitudinal	Adaptive behavior	Functional decline strongly associated with dementia
Cosgrave, et al., 1999	N = 128, mean age 49; 30 had dementia	Cross-sectional	Adaptive and maladaptive behaviour	Increased self-abusive behavior and decreased social engagement predicted by dementia
Cosgrave, et al., 2000	N = 80, females only, age 35 – 71; 35 had dementia	Longitudinal	Adaptive behavior & cognitive symptoms	Identified trigger symptoms and symptoms associated with progression (see text)
Devenny, et al., 2000	N = 66, mean age 53; 10 with cognitive decline and 12 with dementia	Longitudinal	Sequence of cognitive decline	Memory decline predominant, with progressive involvement of other cognitive functions
Nelson, et al., 2001	N = 26, mean age 40 (9 classified as “probable dementia”)	Longitudinal	Neurological abnormalities, emotional and cognitive symptoms; neuro-imaging	Brain atrophy on MRI and abnormal frontal reflexes associated with emotional and cognitive symptoms
Puri, Ho, & Singh, 2001	N = 68, age 29 – 83 (?n with AD)	Unknown	Epilepsy	Late onset but not young onset epilepsy associated with dementia
Tyrrell, et al., 2001	N = 285, age 35-74; 38 with dementia	Cross-sectional	Clinical characteristics	Dementia associated with onset of epilepsy (OR = 9.6) & myoclonus
Devenny, et al., 2002	N = 94, mean age 55; 19 with dementia	Longitudinal	Memory; cognitive assessment	Memory decline present several years before dementia diagnosis
Krinsky-Mchale, et al., 2002	N = 85, 14 had dementia	Longitudinal	Memory and cognition	Verbal explicit memory deficits demonstrated in early dementia
Prasher, et al., 2004	N = 48, age 41-60; 24 with dementia	Longitudinal	Body weight; physical assessment	Ageing associated with weight loss; more if dementia
Huxley, et al., 2005	N = 34, mean age 53; 15 diagnosed with dementia	Cross-sectional	Maladaptive behavior	More frequent and severe behavior problems in dementia
Ball, et al., 2006	N = 55, age 37 - 72; 10 had dementia	Longitudinal	Personality or behavior & cognitive change	Behavior changes and executive dysfunction occur early
Deb, Hare, & Prior,	24 caregivers of adults with	Qualitative study	Caregiver report of early	See text

2007	DS and dementia		symptoms of dementia	
Margallo-Lana, et al., 2007	N = 92, median age 38 at entry; 18 incident cases	Longitudinal (15 years)	Caregiver report and cognitive assessment	Neurological signs are common; neuropathological findings
Ball, et al., 2008	N = 103, aged 36 – 72; 25 had dementia	Cross-sectional	Executive dysfunction, memory and personality change	Informant reported personality changes accords with executive function deficits
Urv, et al., 2008	N = 251, age 45 and older; 38 with dementia	Longitudinal	Maladaptive behavior	See text

Diagnostic criteria for dementia in adults with ID

Given the difficulty in demonstrating cognitive deficits in adults with ID and the differences in presentation when compared to the general population, it is important to investigate the performance of diagnostic criteria for dementia in this population. A previous working group recommended the use of ICD10 criteria (Aylward, et al., 1997) as these put more emphasis on non-cognitive symptoms such as emotional lability and apathy, which are often prominent signs of dementia in adults with ID. ICD10 dementia criteria have been modified for use in adults with ID (DC-LD criteria) (Cooper, Melville, & Einfeld, 2003).

Several studies have systematically investigated dementia diagnostic criteria in older adults with ID. Clinical judgment, based on ICD10 criteria, resulted in more adults with DS diagnosed with dementia than methods based on test batteries (Burt, et al., 2005a). Memory decline was the most commonly met criterion. Similar to the general population the criterion for emotional and behavioral change was met less often (Burt, et al., 1998). Holland et al. (1998) found that DSM IV and ICD10 AD criteria diagnosed the same adults with DS with dementia, but CAMDEX AD criteria were more inclusive. Strydom et al. (2007) compared ICD10, DSM IV and DC-LD criteria in a sample of older adults with non-DS ID. Although correlations between the criteria were good, DSM IV criteria diagnosed more participants with dementia than ICD10 criteria. ICD10 criteria excluded several cases with moderate to severe dementia. Behavioral and emotional changes, a requirement for diagnosis according to ICD10, were not good at discriminating those with and without dementia, and reduced the number of people diagnosed using ICD10 criteria.

Conclusions

Over the past ten years there have been many cross-sectional and longitudinal studies on the prevalence, incidence and presentation of dementia in adults with ID. This has contributed to our knowledge of the disorder in this population. In particular, we have a better understanding of the early symptoms and course of dementia, especially in adults with DS. However, there have been few comparisons on the presentation of dementia between adults in the general population, and adults with DS and non-DS ID. Such comparisons are important for clinical as well as theoretical reasons. The presentation and epidemiology of dementia subtypes other than AD also require more attention in the future.

It has been established that in adults with Down syndrome, signs and behaviors associated with dementia of Alzheimer's type (or other subtypes such as fronto-temporal dementia) emerge during the 5th and 6th decades in approximately one in three of these adults. Age of onset was in the mid 50s, much younger than in the general population. The prevalence increases to the age of 60, but appears to fall after this, possibly due to the increased mortality

associated with dementia where the mean time to death may be as short as 3 to 4 years after diagnosis. Incidence rates show no decline with aging. A significant proportion of older adults with DS never develop clinical signs of dementia.

Some studies have shown an increased prevalence of dementia in adults with ID who do not have Down syndrome, while others have demonstrated rates similar to that of the general population. This may be explained partially by the fact that some studies included all dementia subtypes, while others focused on AD. The severity of ID in the participants may also be a factor since it is difficult to diagnose dementia in adults who are more disabled. The age of onset (approximately 67 years) was slightly younger than in the general population.

Despite progress in our knowledge of the epidemiology of dementia in ID, there are still many differences in the findings between studies which appear to be a reflection of how representative the samples are, the type of study (cross-sectional or longitudinal), identification of possible cases, and the different diagnostic criteria used. The variation in findings and methodology was particularly prominent in the results obtained from the small number of studies in adults with ID who do not have Down syndrome.

In the future, larger studies with representative samples using comparable ascertainment and diagnostic methods, and a good description of participants, could clarify these findings. Agreement between researchers on the use of instruments and criteria will help to reduce variation between studies, and enable us to show potentially important temporal, geographical or between-group differences in the epidemiology of dementia. Another area for future studies is to identify biological and/or environmental factors that increase or decrease the risk of age-related functional decline in people with ID. This is an important area of inquiry as it may inform the development of preventative treatments and programs.

It is surprising that aging and cognitive functioning has been studied in so few of the ID syndromes other than DS, for example, we did not find any dementia studies in even relatively common syndromes such as Fragile X Syndrome. This is a neglected area but potentially very interesting, as it might help to highlight variation in biological aging and its impact on cognitive functioning due to genetic or other factors. Since these special populations are often very small, it will require regional and international collaborations. The challenge for the next decade is to undertake high quality, large-scale collaborative studies of aging and cognitive functioning in the ID population.

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