Syndrome-specific ageing

One of the topics at the Edinburgh Roundtable is on ageing in specific syndromes. In the presentation we will briefly introduce the topic, give an example of a study on ageing in Prader-Willi syndrome and put up questions for possible future research. As introduction to the topic and discussion, we include below the text on dementia in specific syndromes. This text is derived from the SSCA-litterature review of Strydom and colleagues (2009). It focuses only on dementia. However, in our presentation we also will pay attention to other aspects of ageing.

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Dementia in specific ID syndromes other than DS

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Introduction
In the lead up to the 13th World Congress of IASSID (2008), the Special Interest Research Group on Ageing in Intellectual Disability sought to review the state of recent literature on aspects of ageing. The full paper reports on the epidemiology and diagnosis of dementia in people with ID – there is an accompanying paper on
management of dementia and care-giving issues, and others on physical health and ageing (Haveman et al., 2009; see www.iassid.org/iassid/content/view/39/55/).

This present text is part of the report and focuses on genetic syndromes and their association with dementia.

**Aims of the review**

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

1. epidemiology, with a specific focus on genetic syndromes (other than Down syndrome) and their association with dementia;
2. presentation and symptoms;
3. the assessment and diagnosis of dementia in this population.

This present text was derived from the full text and focuses on genetic syndromes other than Down syndrome (DS) and their association with dementia (see aim 1).

**Method: Systematic literature search**

We undertook computerized searches of Medline, EMBASE, and Psychinfo using the exploded MESH term “mental retardation” combined (using the AND function) with the exploded MESH term “dementia”. The search was limited to publication dates from 1997, and was undertaken at the end of April 2008. 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 to develop dementia.
Results: 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. 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 may include Cockayne syndrome, Rett syndrome and Sanfilippo syndrome. Cockayne syndrome (Progeria-Like-Syndrome) is a rare autosomal recessive disorder, but not associated with ID. It 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. Onset of clinical features usually occurs between 2 and 6 years; severe neurological degeneration occurs in most patients 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, patients survive into midlife. 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 the 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 (Devenny, Krinsky-McHale, Kittler, Flory, Jenkins, & Brown, 2004). 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).
Conclusions

It is surprising that aging and cognitive functioning has been studied in so few of the ID syndromes other than DS; for example, we were not able to 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.

References