
Editorial

Down's syndrome and the links with Alzheimer's disease

Down's syndrome is a developmental disorder recognisable at birth and due to the inheritance of an extra copy of chromosome 21 (in 95% of cases) as a result of chromosomal non-dysjunction during meiosis. By contrast, Alzheimer's disease presents predominantly in later life. Although it might seem unlikely that these two disorders are connected, it is clear that probably all those with Down's syndrome over the age of 35 develop the characteristic neuropathological features of Alzheimer's disease and many consequently develop dementia. The relation between these two disorders has therefore been an increasingly productive area for research. The combination of neuropathological and clinical studies has provided the basis for considering the question of why trisomy 21 results in an increased risk for Alzheimer-like neuropathological changes and the eventual development of Alzheimer's disease. Understanding this link is particularly important because of the much improved life expectancy of people with Down's syndrome from a mean of nine years in 1929¹ to over 40 years at present.² An increasing number of people with Down's syndrome are living to an age, which for them, is associated with a significant risk of dementia.

Increasing age is the most important risk factor for dementia of the Alzheimer's type in both the general population and in people with Down's syndrome. In the general population prevalence rates of dementia (including Alzheimer's disease) increase from under 2% in those aged 65-70 years to 10% in those over 85 with incidence rates of 2-3% in those of 75-80 years and roughly doubling with every five year increase in the age group.³ Other factors may increase the relative risk including a history of depression, thyroid disorder, or head injury.⁴ As well as the increased risk in Down's syndrome, two other factors are also recognised to be of particular importance—namely, a family history of presenile dementia⁵ and the inheritance of the ApoE4 allele.^{6,7}

Numerous neuropathological studies have reported that age related increases occur in plaque and tangle formation in people with Down's syndrome and that most people with Down's syndrome who died over the age of 30 had Alzheimer-like neuropathological changes.⁸⁻¹⁰ In the largest of these studies Malamud¹¹ investigated 251 people with Down's syndrome, 20 of whom were over 37 years of age at the time of death. All the older group had Alzheimer-like neuropathological changes. The risk of such changes has been shown to be specific to Down's syndrome and not found in those with learning disabilities of differing aetiologies. Subsequent studies have in general confirmed the similarities between the neuro-

pathological changes seen in Down's syndrome and in Alzheimer's disease. The distribution of the Alzheimer-like changes were similar in both groups and predominated in the amygdala, hippocampus, and association areas of the frontal, temporal, and parietal cortex.¹² The same neurotransmitter changes were also reported.¹³ Antigenic properties of both plaques and tangles were similar¹⁴ as was their structure, studied by electron microscopy.¹⁵ Differences have also been found. Two patients with Down's syndrome were reported to have a greater proportion of amorphous plaque cores than is normally found in Alzheimer's disease¹⁶ and a later study by Mann¹⁷ suggested that senile plaque density in the temporal cortex of people with Down's syndrome is less than that found in age matched patients with Alzheimer's disease. To what extent such differences reflect different pathological processes or differences due to the influence of pre-existing developmental abnormalities affecting synaptogenesis and dendritic structures in Down's syndrome¹⁸ remains unanswered. The value, however, of having a group easily identifiable from birth with such high rates of Alzheimer-like neuropathology has been that the neuropathological changes which ultimately lead to the Alzheimer neuropathology can be identified. In Down's syndrome these start with cerebral amyloid deposition (from as early as 10 years of age) and extend to oligosaccharide deposition and to the ultimate development of plaques followed by tangle formation and cell death.^{19,20}

Heston *et al*⁵ reported a possible further association between these two disorders. In their study of families with Alzheimer's disease they not only found increased rates of dementia in the relatives of the 125 neuropathologically confirmed cases of Alzheimer's disease but also more births with Down's syndrome than would normally be expected. A subsequent study by Whalley²¹ did not replicate this finding but a second American study also found increased births with Down's syndrome in families with Alzheimer's disease.²² On the basis of these findings Berr *et al*²³ hypothesised that increased rates of Alzheimer's disease should be found in families of people with Down's syndrome. In their study of first and second degree relatives of 188 patients with Down's syndrome and 185 learning disabled "controls" no such excess was found. The concept of a shared genetic susceptibility for both Down's syndrome and Alzheimer's disease was also proposed by Schupf *et al*.²⁴ In their study of first degree relatives of 96 adults with Down's syndrome and 80 adults with learning disabilities due to disorders other than Down's syndrome they reported an increased risk of

Alzheimer's disease specifically in women who had had a child with Down's syndrome before the age of 35. There was no such increased risk in older mothers, mothers of children with other developmental disabilities, or in fathers. The relevance of these findings has been challenged²⁵ and further study is required to establish whether they are correct. The neuropathological findings and the family studies of Heston *et al* taken together gave rise to the hypothesis that chromosome 21 might be a possible locus for a "candidate gene" for familial Alzheimer's disease. This has proved correct. Linkage to a chromosome 21 marker in families with early onset Alzheimer's disease was reported²⁶ and the gene coding for the β amyloid precursor protein (APP) has been found on chromosome 21 (q11-q22).^{27,28} Despite some initial apparent contradictory findings, which were shown to be due to aetiological heterogeneity,²⁹ the linkage and the site of the APP gene were shown to be the same and mutations in this gene, in cases of familial early onset Alzheimer's disease, were found.³⁰

Although the neuropathological studies have in general been in agreement, the extent to which these neuropathological changes resulted in cognitive decline and the eventual development of dementia is less certain. Case reports of people with Down's syndrome indicated that in some cases there was clear evidence of behavioural and cognitive changes and loss of skills compatible with dementia³¹⁻³³ but similarly anecdotal reports suggested that this was not as universal as might have been expected on the basis of the neuropathological findings.³⁴ The early more systematic studies of cognitive decline in patients with Down's syndrome used cross sectional designs to examine differences between age groups.^{35,36} These studies showed a number of group differences in orientation, memory, language, attention span, and other areas of cognitive function. For example, Haxby³⁶ compared non-demented and demented elderly people with Down's syndrome and younger people with Down's syndrome with a battery of neuropsychological tests including assessments of daily living skills and tests of immediate memory span, ability to commit new information to long term memory, language function, and visuo-perceptual discrimination and visuospatial construction. Age related changes in new long term memory and visuospatial construction were noted. Performance on tests of immediate memory span and language were unaffected. Those with dementia performed poorly on all tests. In such cross sectional studies, however, the conclusion that the poorer performance of the older age groups was due to the development of dementia had to be tempered by the acknowledgement of cohort effects inherent in the design of the study and may be particularly pertinent to this population because of institutionalisation. An accompanying problem arises with the extreme variability in pre-existing cognitive impairment before possible decline. This means that poor performance at a single assessment may not be unequivocally attributed to decline.³⁴ These two factors have promoted the value of longitudinal designs to allow the profile of decline to be clarified and correlated with physical indices of decline or neuropathology at postmortem. Such studies have shown that the clinical features of dementia in people with Down's syndrome increase with aging, from 8% between 35 and 49 years of age to 75% in those over 60 years.^{10,37} Evenhuis³⁸ in a prospective longitudinal study followed up 17 older people with Down's syndrome until their death. Fifteen of the 17 developed dementia with a mean age of onset of 51.3 years in those with mild learning disabilities and 52.6 years in those with more severe pre-existing disabilities.

As well as the characteristic features of dementia the onset of epilepsy seems to be an important marker of developing dementia in Down's syndrome.³⁹ Prasher and Corbett⁴⁰ investigated the relation between seizures and dementia in 19 people with Down's syndrome who had died. Nine of the 11 who were retrospectively diagnosed as having dementia had developed seizures during the course of their dementia. The authors concluded that the seizures starting in later life "are a strong indicator of a dementing process" and also a sign of a poor prognosis.

The methods of assessment used, potential selection effects resulting from the methods of ascertainment, and the lack of standardised assessment instruments to identify cognitive decline and confirm dementia in a population of people with a pre-existing learning disability has meant that results cannot easily be compared across studies. More standard methods of assessment are, however, being developed and detailed longitudinal studies undertaken. Generally these studies are confirming the findings of early cross sectional designs and show the pattern of decline to be similar to that experienced by those who do not have Down's syndrome or a pre-existing cognitive impairment. Further population based studies are required to be certain of the age specific rates of dementia in an unselected population of people with Down's syndrome. Such epidemiological studies are now becoming more feasible with the development of the new assessment techniques which are appropriate for people with a pre-existing learning disability.

The developing brain scanning technologies have also been used to compare the brain changes in Down's syndrome with those found in people with Alzheimer's disease. Schapiro *et al*⁴¹ studied 20 young adults and nine older adults with Down's syndrome compared with aged matched controls using PET and CT techniques. The patients had been assessed with a battery of established neuropsychological techniques. The PET studies showed similar abnormal patterns of glucose utilisation in parietal and temporal neocortices as was found in Alzheimer's disease in the general population as well as, on CT, evidence of progressive cerebral atrophy in those patients with Down's syndrome and dementia. An MRI study⁴² also reported evidence of significant cerebral ventricular enlargement and reduction in hippocampal size with increasing age in people with Down's syndrome. Those with Down's syndrome between the ages of 23 and 51 and no dementia did not have general features of cerebral atrophy. Two patients, however, had clear evidence of dementia and in these patients the changes were particularly pronounced. This supports the findings of the study by Schapiro *et al*⁴³ which suggests that significant atrophy only becomes apparent when the clinical features of dementia have developed. Proton magnetic resonance spectroscopy (MRS) has also been used to investigate age related brain changes in Down's syndrome. Murata *et al*⁴⁴ studied 18 people with Down's syndrome between 20 and 46 years of age and aged matched healthy controls. No age related differences in the ratio of N-acetylaspartate (NAA), total creatine (Cr), and compounds containing choline (Cho) were found in the controls. In the Down's syndrome group, however, the ratios Cho/Cr and NAA/Cho were significantly increased in those in their 40s. They propose that these changes are indicative of degeneration and/or rapid synthesis of brain cell membrane. To test the hypothesis that this is due to premature aging these findings need to be compared with an elderly general population group with and without evidence of dementia.

Studies with different methodologies have convincingly showed that people with Down's syndrome are at

high risk for age related brain changes, cognitive decline, and dementia at a relatively early age. The important findings relating to the APP gene on chromosome 21 have led to the proposal that excess amyloid production or abnormalities in the processing of amyloid and its subsequent deposition are central to the pathological mechanism underlying the aetiology of Alzheimer's disease in general.⁴⁵ More conservatively it has been argued that " β amyloid deposition is a necessary but not a sufficient factor for the pathogenesis of Alzheimer's disease".⁴⁶ Rumble *et al*⁴⁷ reported that serum amyloid concentrations were raised in patients with Down's syndrome, as would be expected from a gene dosage effect, but similarly high concentrations were not found in people with Alzheimer's disease without Down's syndrome. Royston *et al*⁴⁸ studied the relation between diffuse and classic plaques, the amyloid load in the temporal cortex of 21 people with Down's syndrome who had died between the ages of 13 and 65 years, and the extent of dementia. The dementia was assessed retrospectively from the case notes. They reported a significant relation between the extent of amyloid deposition and the presence of dementia. The retrospective identification of dementia from case notes is likely to have been problematic, however, and the authors did not examine other neuropathological changes that may have also been associated with the clinical features manifested. Alternative explanations for the neuropathological basis of Alzheimer's disease have centred on changes in the tau protein which, it has been argued, is an important neuropathological event leading to neuronal cell death and dementia.^{49,50} This has more recently become the focus of study in Down's syndrome. The level of paired helical filament tau protein has been reported to be the same in the brains of people with Down's syndrome with and without dementia; however, the level of normal tau protein was significantly reduced in those with Down's syndrome and dementia.⁵¹ The authors of this study argued that the redistribution of the types of tau protein in Down's syndrome may be the relevant event associated with dementia.

The amyloid and tau protein arguments are likely to continue. Consideration also needs to be given to the issue of "aging". Martin⁵² proposed that Down's syndrome was associated with premature aging. Is what is found in Down's syndrome fundamentally the consequence of aging and is Alzheimer's disease part of the process of aging rather than a discrete disease entity? If this is the case then research should again focus on the reasons for the shortened lifespan and other age related changes in Down's syndrome. The role of superoxide dismutase, the gene for which is on chromosome 21 and the activity of which is increased in Down's syndrome,⁵³ should be re-examined in the light of the free radical theories of aging and proposals that amyloidosis and free radical activity may be associated.⁵⁴ Increasing age in Down's syndrome is also associated with increasing rates of depression,⁵⁵ thyroid dysfunction,⁵⁶ and sensory impairments.⁵⁷ These factors are important diagnostically as they can both present in a manner similar to dementia or coexist with dementia and contribute to the severity of the disability.⁵⁸

There are important questions in Down's syndrome research that require answering. In the field of neuropsychology there are now two main tasks. Firstly, the continuing development of neuropsychological assessments which are both sensitive to change and applicable to patients with substantial pre-existing cognitive impairments and, secondly, the development of tests which are highly predictive without the need for numerous serial assessments. If such assessments become available, they

will make large contributions to the quality of research and clinical diagnosis. This in turn will enable the amalgamation of the neuropathological and clinical findings and the further exploration of the role of other putative risk factors for Alzheimer's disease in the Down's syndrome population. For example, the presence of ApoE 4 influences the age of onset of Alzheimer's disease in the general population and has been reported to effect the life expectancy⁵⁹ and possibly the Alzheimer-like neuropathological changes in people with Down's syndrome. Whether other risk factors such as past head injury or the level of pre-existing learning disability has an influence is not known. Prasher,⁶⁰ linking clinical and neuropathological findings, described a clear temporal relation in Down's syndrome between the increasing level of neural plaque formation with age as described by Mann¹⁷ and a rapid increase in the presentation of dementia 10 years later. It is the explanation of the events occurring during this period which are critical in understanding the neuropathological changes associated with cognitive change on the one hand, and those which result in neuronal cell death and the clinical features of dementia on the other. Progress therefore needs to be made on several fronts. The recognition of dementia and its management needs to be improved both for the purposes of research and in service delivery. The role of amyloid, premature aging, and tau protein changes need to be elucidated and the relevance or not of other risk factors established. The ultimate goal must be the development of preventive treatment strategies. These can only be rationally developed on the basis of a clear understanding of the pathological processes involved.

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NEUROLOGICAL STAMP

Hyoscyamus niger (henbane)

Henbane belongs to the solanaceae family. The narcotic alkaloids hyoscyamine, scopolamine, and atropine are derived from this foul smelling weed.

Its name is derived from the Anglo-Saxon Henn (chicken) and Bana (murderer) because when fowls eat the seeds of this plant, they become paralysed and die. The seeds are also poisonous to children, rodents, pigs, and fish. It was a traditional ingredient of witches' brew. All parts of the plant are poisonous and, if eaten, even small amounts cause anything from dizziness to delirium along with other anticholinergic effects. To the Elizabeth herbalist, John Gerard, henbane poisoning seemed akin to alcohol poisoning in that both caused stupor followed by comatose sleep. An Anglo-Saxon text gives the advice "in case a man is not able to sleep, take henbane seed and juice of garden mint, shake them together and smear the head therewith; it will be well with it."

Its flower is pictured with a grinder and pestle and mortar as part of a commemorative set of stamps issued by Czechoslovakia in 1971 for the International Congress of Pharmacology held in Prague. (Stanley Gibbons 1984, Scott 1777).

