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Ageing in Down's Syndrome

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Summary: In a group of 23 hospital patients aged over 50 with Down's syndrome, psychological testing indicated that significant intellectual deterioration, which was un-related to chronological age, sex, length of hospitalisation, or earlier mental age, had occurred in nine. Clinically, there was no evidence in any patient of active physical illness, focal neurological signs, or dementia, but significant associations were found between intellectual deterioration and decreased visual acuity, hearing loss, and macrocytosis.

Down's syndrome is a common cause of mental handicap, affecting approximately one in 600 live births. The life expectancy of these individuals, though reported to be only nine years by Penrose in 1932, is now markedly increased, with many surviving into their fifth decade and a few living beyond 60 years of age (Carter & Jancar, 1983).

Of particular relevance to those involved in the care and training of older Down's syndrome individuals is the compelling neuropathological evidence for a link between Down's syndrome and dementia of the Alzheimer type (DAT), demonstrated by Whalley (1982). Specifically, the neuropathological triad of senile plaques, neuro-fibrillary tangles, and neuronal degeneration which are characteristic of DAT (Lishman, 1978), have been found post mortem in all Down's syndrome individuals beyond the third decade, with senile plaques forming even during the second (Burger & Vogel, 1983). Similar neuropathological features were found in 88.9% of Down's syndrome patients over 30 years of age, 95% over 40 years, and 100% over 50 years by Sylvester (1983). The possibility of an association between Down's syndrome and DAT is of particular importance in the search for aetiological factors in this type of pathology, which may affect over 50% of patients with a diagnosis of dementia.

Since DAT can be defined as a progressive, age-related, chronic cognitive dysfunction (Schneck *et al*, 1982), it might reasonably be supposed that gross cognitive and behavioural deterioration would eventually occur in Down's syndrome patients, especially in those over 50 years of age, whose life expectancy is limited. Clinical impressions, however, are at odds with this hypothesis, since many such individuals maintain good physical and mental health into the fourth and fifth decades of life (Sylvester, 1983).

This paradox between unequivocal neuropathological findings and limited clinical evidence of dementia has been partly resolved by the use of specific neurological and/or psychological assessments to detect age-related deficits, in studies by Owens *et al* (1971), Dalton *et al* (1974), Wisniewski *et al* (1978) and Miniszek (1983). However, although results generally indicate impaired functioning in older as compared with younger Down's syndrome individuals, most studies contain only small numbers surviving into the fifth decade or beyond, and often have no baseline information on previous functional levels against which to compare current findings.

At the Stoke Park Group of Hospitals for the mentally handicapped, baseline data on psychological and clinical aspects have been collected since the 1930's. In January 1984, there were 1,041 inpatients, including 98 with a diagnosis of Down's syndrome of whom 35 were over 50 years of age (Jancar, 1984). Having commenced a programme of systematic research into aspects of ageing in the mentally handicapped, we present here some preliminary findings in relation to Down's syndrome.

Method

Of the 35 Down's syndrome patients over 50 years of age, 11 were excluded due to insufficient baseline data and one due to having had a cerebrovascular accident. The distribution of the remaining 23 patients (14 male, nine female) by chronological age was:— 50–54 years 17; 55–59 years 4; 60–64 years 2. The mean chronological age was 54.3 years, with a range of 50.9–61 years. Mean length of stay in hospial was 40.4 years, with a range of 15.75–54.75 years.

The Stanford Binet Intelligence Scale (Terman & Merrill, 1937) Forms L, M, or L-M had been regularly administered to the entire sample since admission, providing numerous baseline mental age scores for each patient. Mental age assessments earlier than the 20th birthday were excluded from analysis, to allow for the ongoing intellectual development to approximately 16 years of age which was demonstrated in Down's syndrome by Fisher & Zeaman (1970) and by Demaine & Silverstein (1978). Only those who had three or more baseline mental age scores were included in the study; the mean number of

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scores for each patient was 5.4, with a range of 3–11. To provide continuity with earlier measures, patients were re-assessed on the Stanford Binet to obtain a current mental age (MA) score; baseline and final MA scores were thus available for analysis.

Behavioural functioning was assessed using a structured interview with nursing staff which focussed on self-care skills such as toiletting, dressing, washing, and feeding. In the absence of baseline behavioural measures, staff were asked to say whether a particular behavioural problem, if present, represented a deterioration in performance or was part of the patient's usual repertoire.

Clinical assessment included a full physical and neurological examination, and serial recordings at various intervals concerning vision, hearing, blood picture, electrolytes, thyroid function, and electrocardiogram. Abnormalitities in any of these areas were noted and subsequently compared statistically with intellectual status. The clinical and psychological assessments were made independently by assessors who did not know one another's findings.

Results

For the 23 patients, 102 baseline MA scores were available, with a test-retest interval of 3.7 years (range two months to 14 years). The mean test-retest fluctuation in MA was 0.76 months (standard deviation 4.05 months).

The difference between mean MA at baseline and final MA was obtained for each patient. Fifteen showed a decrement in MA (mean 14.97 months, s.d. 19.55), seven an increment in MA (mean 2.18 months, s.d. 1.95), and one remained unchanged.

TABLE

Stanford Binet Intelligence Scale: Mental ages (months)

	Number of baseline assessments	*Mean baseline mental age*	*Current mental age*	*Difference in mental age*
Subject S1	3	37.7	34	−3.7
S2	6	50.0	36	−14***
S3	5	57.8	61	+3.2
S4	5	53.0	44	−9.0*
S5	5	44.6	35	−9.6*
S6	3	29.3	29	−0.3
S7	7	38.7	39	+0.3
S8	5	53.2	54	+0.8
S9	5	34.0	37	+3.0
S10	6	61.8	64	+2.2
S11	4	57.7	52	−5.7
S12	9	70.8	71	+0.2
S13	5	41.4	47	+5.6
S14	7	52.6	47	−5.6
S15	3	38.0	24	−14***
S16	6	60.8	45	−15.8***
S17	4	39.0	26	−13.0***
S18	4	54.2	46	−8.2
S19	3	24.0	24	0
S20	7	80.3	0	−80.3***
S21	5	59.2	46	−13.2***
S22	7	31.0	0	−31.0***
S23	11	48.2	47	−1.2

(*P <0.05, **P <0.01, ***P <0.001)

To determine whether these differences represented a significant fluctuation in MA, the mean MA shift at baseline for the group (0.76 months) was subtracted in each case, and the result transformed into a z-score. Using this method, significant intellectual deterioration was found to have occurred in nine patients, as shown in the Table. In those who showed statistically significant deterioration in MA, the mean decrement was 22.2 months (range 9–80.3 months). The two zero scores on current assessment were due to lack of ability in completion of test items rather than to unco-operativeness or test refusal. None of the incremental scores was significant.

Fisher's exact probability tests were used to identify any associations between intellectual deterioration and (a) sex of patient; (b) chronological age; (c) length of stay; (d) mean MA at baseline. None were significant.

The behavioural data revealed that all the subjects were independent as regards feeding skills; 16 were able to wash themselves independently though seven had to be prompted to wash; 17 were completely toilet trained, five were incontinent of urine, and one had an indwelling catheter. Twenty-one were independent in dressing skills, one required prompting during dressing, and one had to be dressed by nursing staff. Problem behaviours were relatively uncommon and included inactivity (seven), hoarding (six), damage to property (two), social withdrawal (two), and repeatedly ripping up paper (one). Using Fisher's tests, there was no association between behavioural dependency and intellectual deterioration for any of the skill areas, nor were there more problem behaviours amongst the intellectually deteriorated patients.

Staff reported a behavioural deterioration in only three cases. These were (1) incontinence, inactivity, and a longer time taken to make a bed; (2) repeatedly ripping up paper and a longer time taken to eat meals; (3) a longer time to make a bed. Intellectual deterioration was present in cases (1) and (2).

Clinically, it was found that visual acuity was reduced in ten patients, nine of whom had cataracts; hearing loss had been identified in 11. Hypothyroidism had been found in one patient (now biochemically euthyroid following replacement therapy). In the remainder, thyroid function was within normal limits.

Red cell size for the group as a whole was found to be at the upper limit of the normal range (76–96 fentolitres) with a mean value of 95.37 fentolitres, and it was above this value in 11 patients. Minor ECG changes were found in two cases, the remainder being within normal limits. No focal neurological signs were elicited on examination, and there was no evidence of active physical illness in any of the group. Karyotype determination indicated 46,XY/47, XY+21 mosaicism in two males. One patient had a history of epilepsy which was well-controlled by carbamazepine. Two had a history of superimposed functional psychosis which had responded to major tranquillisers.

It was found that the patients with significant intellectual deterioration were more likely to have visual impairment (Fisher's exact probability P <0.0001) or hearing loss (P <0.001).

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All nine intellectually deteriorated patients had erythrocytes larger than the group average, whereas macrocytosis was present in only two non-deteriorated patients.

Discussion

There is convincing evidence from previous researchers (eg Olson & Shaw, 1969) that Down's syndrome patients display the neuropathology of Alzheimer's disease, and that this is more likely to occur in those dying after 35 years of age. It was hypothesised in the present study that those nearing the end of their lifespan would therefore be expected to show the gross cognitive and behavioural deterioration which is characteristic of the disease in the normal population (Lishman, 1978). Baseline psychometric and clinical data for a relatively large sample of Down's syndrome patients living beyond the fifth decade have made possible a rigorous scientific analysis of this issue.

The most striking finding from the psychometric data is that only 39% of 23 patients were intellectually deteriorated to a significant extent, although the degree of deterioration in these nine cases was mostly severe. Three other patients, who were excluded from the study for statistical reasons and who were intellectually and behaviourally regressed on examination, would have raised the proportion of intellectually deteriorated patients to 48%, had they been included.

However, the Stanford-Binet test provides only a global assessment of intellectual functioning, and is not itself a test for dementia. Furthermore, many of the test items are verbally-based, and it is verbal skills which have generally been shown to be resistant to effects of ageing in the normal population, (Schaie, 1980) so that the number of intellectually deteriorated patients in this sample may be an underestimate. A further difficulty lies in the quasi-longitudinal method used here, since one might expect the elderly survivors in such studies to be more healthy than their predecessors. However, we do not regard the main finding as seriously negated, though further studies, perhaps of a cross-longitudinal nature using more sensitive tests of cognitive function, might clarify the position.

At present, it is unclear what happens to Stanford-Binet scores in older mentally handicapped people as a whole. Of the Down's syndrome patients whose MA decrement was statistically significant, it is not possible to say whether their decline is any greater than would be observed amongst a more elderly mentally handicapped sample, though the authors propose to investigate this. Whether a statistically significant MA decrement necessarily has clinical significance, in terms of everyday functioning for the individuals concerned also merits further consideration.

The level of behavioural functioning was generally high in our subjects, with the majority being independent as regards dressing, feeding, washing, and toiletting skills. There were few behavioural problems that could not be attributed to prolonged institutionalisation, eg inactivity. In keeping with previous studies, such as that of Owens *et al* (1971), there was no association between intellectual deterioration and behavioural regression, except in two cases. It has been suggested by Miniszek (1983) that Down's syndrome patients living in hospital may retain their personal integrity, even in the event of DAT, due to their structured lifestyle, although it is still unclear why they do not show behavioural deterioration in the independent performance of self-care skills. It is possible that the intellectually deteriorated patients in this study, even though severely cognitively impaired, were not in the advanced stages of the disease, at which behavioural disorganisation is most likely to occur in other subjects. In this context, it is relevant that the three patients who were demented on clinical examination showed both intellectual and behavioural deterioration.

Intellectual deterioration was found to be independent of the patient's sex, chronological age, length of stay in hospital, and previous intellectual level. The nine intellectually deteriorated patients were therefore not more institutionalised than the remainder, not were they the more intellectually able individuals when they were younger. The independence of intellectual deterioration from chronological age suggests that the cognitive changes may be due to factors other than those simply due to the passage of time.

The clinical findings, and their relationship to intellectual status, are of interest. Since all 23 patients were in generally good physical health and without evidence of focal neurological signs or dementia, it seems unlikely that gross DAT changes were present in any; the patient with epilepsy and the two patients with a history of functional psychosis were amongst those who had remained intellectually stable. It was also evident that intellectual function was independent of renal, cardiac, and thyroid status, which were within normal limits in the great majority.

Various mechanisms may be responsible for the high incidence of visual or auditory deficits and macrocytosis found in these older Down's syndrome patients. It has been suggested by Walford (1980) that the entire syndrome is one of accelerated ageing, and that this reflects an excess loading

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of regulator genes, via the extra chromosome 21, which causes increased enzyme activity and thus reduced cellular longevity. Evidence supporting this theory includes findings in Down's syndrome of elevated erythrocytic enzyme activity by Naiman *et al* (1965), decreased osmotic fragility by Kedziora *et al* (1972), and macrocytosis by Eastham & Jancar (1983), who also showed that macrocytosis occurs in association with anticonvulsant therapy, but since only one patient in our present group had been treated by anticonvulsants, this was not the explanation for the present finding.

Other workers have suggested that localised effects in the brain of Down's syndrome individuals may be of importance. These include a specific deficit of inhibitory activity in the brainstem, resulting in reduced auditory evoked responses, (Gigli *et al* (1984) and basal ganglia calcification (Wisniewski *et al*, 1983).

Whatever the explanation for these clinical aspects of the phenotype, the present study indicated a significant association between intellectual deterioration and their occurrence. It may be that, even in the absence of Alzheimer changes, older Down's syndrome individuals display apparent intellectual decline because of sensory impairments which make for difficulties in everyday function and in the formal testing situation. Alternatively, the intellectual decline may be due to DAT pathology, or to an interaction between this and sensory loss.

The findings reported here are the preliminary results from a larger research programme, and we are presently examining a matched control group of non-Down's syndrome mentally handicapped patients against which to compare the present results. Further research is needed to consider the important question of which other factors differentiate those who decline intellectually, and to investigate the mechanism associating macrocytosis and intellectual deterioration.

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