Identical twins with Alzheimer's disease

CHRISTINE KILPATRICK, RICHARD BURNS, PETER C BLUMBERGS

From the Flinders Medical Centre and the Institute of Medical and Veterinary Science, South Australia

SUMMARY Genetically proven identical twin sisters with Alzheimer's disease are reported. Both sisters at the age of fifty years developed a dementing illness. Their mother and maternal grandmother developed at the same age a similar illness. It is suggested that in some cases of familial Alzheimer's disease the condition is inherited by a single mutant gene.

The aetiology and genetics of both sporadic and familial Alzheimer's disease remain uncertain. There is doubt that a genetic component in true Alzheimer's disease exists and so monozygotic twin studies should help define this. Until now four such studies have been reported.¹⁻⁴ A further report of genetically proven identical twins is presented. Both patients developed at the age of fifty years histologically proven Alzheimer's disease. Their mother and maternal grandmother developed, at the same age, a clinically similar dementing illness.

Case reports

Mrs PG (UR 00 34 64) and Mrs RD (UR 05 59 26) born in 1926 are identical twin sisters (fig 1). Genetic studies reveal a 99.7% probability they are monozygous (table). At the age of fifty years both sisters simultaneously began to lose their intellectual faculties. Initially there was impaired short term memory, which steadily progressed to a global dementia. Six years later they are totally dependent on their respective husbands and are unable to read, write or perform any household duties. They need continuous supervision.

Their mother at the age of fifty years developed a clinically similar dementing illness and died eight years after the onset. A necropsy was not performed but review of her clinical notes suggests she had a progressive dementia beginning with predominantly short term memory loss and progressing to severe intellectual impairment. The description of her mental state was remarkably similar to that of her daughters. Examination, apart from the mental state, revealed no abnormal neurological signs and involuntary movements were not present. The case notes of the maternal grandmother were not available, but it would appear that she had a progressive dementing illness beginning in

her fifties. The twin sisters have two younger sisters who are well. The twin sisters between them have five children, all of whom are well.

On examination (six years after onset of symptoms) both sisters were completely disorientated in time and place with no knowledge of current events. Both had a severe nominal dysphasia, with non fluent speech and were incapable of a rational intellectual conversation. Their short term memory was severely impaired and they were unable to perform simple additions or subtractions. Both had generalised hyperreflexia, primitive reflexes, flexor plantar responses and normal tone and power. There were no involuntary movements and the gait was normal. Both patients were continent. The examination findings of each sister were remarkably similar although Mrs PG demonstrated some emotional lability and Mrs RD had a more severe nominal dysphasia. In May 1982, on the Wechsler Adult Intelligence Scale and Wechsler Memory Scale, Mrs PG had a verbal IQ of 62, a performance IQ of nil, a full scale IQ of 55 and the memory quotient was less than the scales could measure. Mrs RD had a verbal IQ of 63, a performance IQ of 59, a full scale IQ of 59 and the memory quotient of 54. Although the pattern of intellectual impairment of both sisters was similar, Mrs PG was more severely affected with virtually total short term memory loss. Psychometric testing had been performed in October 1980 and compared with the result of 1982, both sisters had shown significant intellectual deterioration. Full blood examination, serum B12, serum folate, thyroid function tests and VDRL were within normal limits. The electroencephalogram of each patient was abnormal with a generalised disturbance of cerebral function. The CT scans were performed in October 1980 and May 1982. The scans showed mild cortical atrophy and minimal ventricular dilatation with no significant difference between 1980 and 1982. Both patients had a brain biopsy via a frontal burr hole.

The frontal cortical biopsies from both sisters (figs 2, 3) were similar showing severe cortical neuronal loss and neurofibrillary tangles in many of the remaining neurons. Numerous senile plaques often with central amyloid cores, were present throughout the cerebral cortex. There was prominent cerebrovascular amyloidosis of the leptomeningeal and superficial cortical blood vessels. The vessels were Congo red-positive, displaying apple-green bire-

Address for reprint requests: Dr RJ Burns, Department of Medicine, Flinders Medical Centre, Bedford Park 5042, South Australia, Australia.

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Fig 1 Twin sisters, Mrs RD (left) and Mrs PG (right).

Table Zygoty tests

Character and phenotype		Relative probability of dizygoty
Prior probability		2.33
Like sex		0.50
<i>Blood Groups</i>		
1 ABO	0	0.69
2 RH	Rlr (CDe/cde)	0.54
3 K	Kk	0.55
4 FY	AB	0.65
5 MNS	MNSs	0.46
6 P	P1	0.85
<i>Red Cell Enzyme</i>		
7 ACP1	Polymorphisms	
8 GLO1	B	0.65
9 ESD	12	0.63
10 PGM1	1	0.90
11 GALT	2	0.81
	N	0.93
<i>Serum Protein</i>		
12 HPA	Polymorphisms	
13 GC (subtyped)	12	0.62
14 C3	1S2	0.63
15 PI (subtyped)	2	0.77
16 TF (subtyped)	M1	0.70
	C1	0.80
Relative probability of dizygoty:		0.0028
Probability of monozygoty		=0.9972

Fig 2 Section of frontal cortex of sister PG showing three neurofibrillary tangles and senile plaque (Glees-Marsland silver impregnation method, original magnification $\times 1250$).

Fig 3 Frontal cortex of sister RD showing neurofibrillary tangle (Glees-Marsland silver impregnation method, original magnification $\times 1250$).

fringe in polarised light; electron microscopy confirmed the presence of fine nonbranching fibrils 8 nm to 10 nm in diameter consistent with amyloid.

Discussion

To our knowledge this is the first report of genetically proven identical twins concordant for Alzheimer's disease. Cook *et al*⁴ reported twins of identical appearance with Alzheimer's senile dementia, but genetic identity was not proven. The relatively early and almost simultaneous onset of dementia in these sisters together with a positive family history makes it highly unlikely this concordance is coincidental and suggests autosomal dominant inheritance.

The interest in this report stems from the doubt concerning the nature of a genetic component in the aetiology of Alzheimer's disease. Approximately one-third of cases are estimated to be familial and it is therefore surprising that so few twin studies have been reported.⁵ Familial cases differ clinically and probably in aetiology from sporadic Alzheimer's disease. They tend to have a more youthful onset and a more rapid course.⁵ Symptoms first occurring after the age of seventy years carry little risk to close relatives.⁵ Most familial cases do not show a pattern of dominant inheritance and there is no doubt that in most cases, Alzheimer's disease is not inherited as a single mutant gene, and other aetiological factors predominate. This concept is strengthened by the two reports of discordance for the disease in monozygotic twins.^{2,3} Cook *et al*,⁴ however, have cast doubt on the validity of these reports. The twin sisters reported by Davidson² lacked laboratory evidence of uniovularity and it is suggested that the follow up period in both reports was too short to completely exclude concordance. In the twins reported by Cook *et al*,⁴ nine years lapsed between the diagnosis of each twin.

To account for familial incidence and twin discordance, patients with Alzheimer's disease have been studied to identify other contributing factors. It has been suggested that disease susceptibility may be linked to immunogenetic markers within the HLA complex.⁶ Henschke *et al*⁶ and others^{7,8} have studied HLA antigens but most have not found a significant association between Alzheimer's disease and the HLA system.

The role played by chromosomal abnormalities remains unresolved. It is recognised that almost all people with Down's syndrome over forty years of age develop an Alzheimer's-like disease.^{9,10} Heston *et al*⁵ found an apparent increased incidence of Down's syndrome among relatives of patients with Alzheimer's disease. This association led to the

finding of an increased incidence of lymphomas in relatives of patients with Alzheimer's disease. The genetic significance of these relationships however is uncertain.

Finally, it has been suggested that familial Alzheimer's disease may be a transmissible dementia.¹¹ There are clinical, pathological and epidemiological similarities between Alzheimer's disease and the transmissible dementia Creutzfeldt Jakob disease. Cases of Creutzfeldt Jakob disease and familial Alzheimer's disease occurring in the one family have been reported.^{11,12} A spongiform encephalopathy has developed in primates inoculated with brain tissue from a patient with familial Alzheimer's disease.¹² Diseases attributable to a slow virus may mimic the pattern of autosomal dominant inheritance as occurred with the transmission of Kuru in New Guinea. It is possible therefore that some cases of familial Alzheimer's disease apparently resembling autosomal dominant inheritance may in fact be due to a transmissible agent such as a slow virus or that genetic factors may control the response to a slow virus and therefore determine which family members will be affected.

The development of histologically proven Alzheimer's disease in genetically proven identical twin sisters together with a history of a similar dementing illness in the mother and maternal grandmother supports the suggestion that at least in some cases of familial Alzheimer's disease, the disorder is inherited by a single mutant gene.

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