J Neurol (2001) 248:45–50

ORIGINAL COMMUNICATION

E. K. Warrington
S. K. Agnew
A. M. Kennedy
M. N. Rossor

Neuropsychological profiles of familial Alzheimer's disease associated with mutations in the presenilin 1 and amyloid precursor protein genes

Received: 25 April 2000
Received in revised form: 26 June 2000
Accepted: 14 July 2000

E. K. Warrington (✉) · S. K. Agnew
A. M. Kennedy · M. N. Rossor
Dementia Research Group
Department of Clinical Neurology
Institute of Neurology
Queen Square
London, WC1 N 3BG, UK
Tel.: +44-20-78 37 36 11, ext 36 39
Fax: +44-20-72 09 01 82

Abstract Patients with familial Alzheimer's disease and a subset known to have presenilin mutations were compared with sporadic cases on a comprehensive battery of cognitive tests. These included measures of memory, intelligence, language and perception. The three groups were very comparable, in terms of severity, on global measures of dementia. However, their profiles/patterns of cognitive impairment differed in two respects; the group with sporadic Alzheimer's disease were significantly more impaired on tests of object naming and object perception than either the group with familial Alzheimer's disease or group with familial Alzheimer's disease and presenilin mutations, yet they scored at a significantly higher level on the measure of verbal intelligence. This study provides further evidence of the heterogeneity of the disease process.

Key words Neuropsychology · Familial Alzheimer's disease

Introduction

Alzheimer's disease (AD) is a common disorder of late life and is characterised by an insidious onset of memory impairment progressing to dementia, in association with the histopathological features of senile plaques and neurofibrillary tangles. Clinical heterogeneity, however, is observed with respect to the pattern of cognitive impairment, the age at onset and the presence of AD in the family history. The latter is common, and in rare instances familial AD (FAD) may occur as an autosomal dominantly inherited disorder of early onset. Autosomal dominant inheritance has been considered as a determinant of clinical heterogeneity, and differences in cognitive profile have been sought between FAD and sporadic AD (SAD) [1–5]. However, non-systematic cognitive testing and the genetic heterogeneity of FAD has made interpretation of results difficult.

The genetic heterogeneity of FAD has been clarified by the identification of mutations in the gene for amyloid precursor protein (APP) and in the presenilin (PS) 1 and 2 genes, all of which are reported in association with autosomal dominant FAD [6]. Some early onset FAD pedigrees do not appear to be associated with mutations in either the APP or the PS genes, suggesting at least one additional genetic locus. The apolipoprotein E4 allele is a risk factor for the development of AD [7–9].

Early comparisons between FAD and SAD inevitably grouped patients in the absence of knowledge of the underlying genetic status, but nevertheless reported differences. Thus Breitner and Folstein [2] reported that prominent aphasia and apraxia were more frequent in cases with a family history of AD. This observation was based on a clinical assessment rather than formal neuropsychological test results, and subsequently, when disease severity was taken into account, this pattern of performance was not confirmed [10].

The first detailed comparison of cognitive functions, including tests of memory, language function and visuospatial skills, failed to find any difference between cases of FAD and SAD [1]. However, there were only seven familial cases belonging to two pedigrees, albeit with an autosomal dominant pattern of inheritance. A more re-

JON 371

cent paper comparing FAD and SAD cases considered the issue of the criteria for determining a family history [11]. Three groupings of familial cases were identified: those with one or more affected relatives, those with a 90 % probability that multiple affected family members had not aggregated by chance, and those cases with a definite autosomal dominant pattern of inheritance. A comparison of SAD and FAD cases yielded very few significant differences. Indeed the only finding of note was a higher *naming score* in a familial group (cases with 90 % probability).

A further problem in comparing neuropsychological profiles concerns the psychometric properties of the test battery. Multiple domains of cognitive function are impaired in AD. Any meaningful comparison of neuropsychological profiles must ensure that each cognitive domain be assessed on an equivalent scale. Spinnler and Della Sala [12], the first to address this issue, developed a procedure for comparing performance across tests by deriving 'grade' scores (a 5-point scale) by reference to the percentile distribution of scores of a standardisation sample. Fox et al. [13] extended this methodology to derive an overall measure of severity.

The present study compares the cognitive performance of a group of young onset autosomal dominant FAD (*PS–1* and *APP*) patients and a group diagnosed with SAD on a comprehensive battery of neuropsychological tests that probed each of the major domains of cognitive function. A subgroup of the FAD cases was known to have *PS–1* gene mutations and this genetically homogeneous group of familial cases (FAD PS–1) is also compared with the sporadic cases.

Procedures

Patient Groups

The diagnosis of AD was ascertained by a full medical and neurological examination and each individual fulfilled the NINCDS-ADRDA criteria for probable AD [14]. For each individual a detailed family history was obtained. In the FAD group the diagnosis of AD was confirmed at autopsy in at least one family member.

Group 1: autosomal dominant Alzheimer's disease

These patients were identified by the Dementia Research Group at St. Mary's Hospital and the National Hospital for Neurology and Neurosurgery on the basis of a positive history of AD, developed at a young onset, in at least three members of the family, spanning at least two generations. Twenty-four patients (11 males and 13 females) who fulfilled these criteria and who were able to complete the neuropsychological assessment were identified from 13 families. These patients all fulfilled the NINCDS-ADRDA criteria for probable AD. Six patients from four families (three with APP V717I; and one with 1 APP V717G) had *APP* mutations. Thirteen patients from six families were found to be associated with mutations in the *PS–1* gene [eight from two families with PS–1 M139V; one from one family with D4, one with I143F; one with E120K; one with L250S and one with a splice acceptor site mutation (S290C, Δ9)]. Genotyping involved direct gene sequencing in affected individuals as previously described [15–17]. The performance of these 13 patients (FAD PS–1) was analysed separately. The mean age of the FAD group was 47.3±7.9 years and that of the smaller subset FAD PS–1 was 45.2±8.4 years.

Group 2: sporadic Alzheimer's disease

Twenty-six patients (16 males and 10 females) attending the Specialist Cognitive Disorders clinic at the National Hospital, Queen Square, who fulfilled the NINCDS-ADRDA criteria for probable AD, had no family history of dementia in any first- or second- degree relative and had the clinical diagnosis of SAD. The mean age of this group was 62.8±.6.1 years.

All patients underwent a full general physical and neurological examination, which included visual acuity assessed using the Snellen chart, routine blood tests, and magnetic resonance imaging [18]. The neuropsychological assessment was carried out at the time of presentation when probable AD was diagnosed. No patient had significant additional neurological or medical illness [14]. In particular, no patient had evidence of significant vascular disease and all scored less than 4 on the Hachinski et al. [19] scale.

Neuropsychological battery

Tests for which standardised scores were available, and which targetted a specific domain of cognitive function were selected. Each patient attempted the following battery of neuropsychological tests administered by a psychometrician:

- Reading: National Adult Reading Test (NART) [20]
- Verbal intelligence: WAIS-R VIQ (short version: vocabulary, similarities, digit span and arithmetic) [21]
- Non-verbal intelligence: WAIS-R PIQ (short version: picture completion, picture arrangement and block design) [21]
- Verbal memory: RMT Words [22]
- Visual memory: RMT Faces [22]
- Naming: Graded Naming Test (GNT) [23, 24]
- Arithmetic: Graded Difficulty Arithmetic Test (GDA) [25]
- Spelling: Graded Difficulty Spelling Test (GDS) [26]
- Object perception: VOSP Silhouettes [27]
- Information processing speed: Digit Copying [28]

Further details of this battery are given in Fox et al. [29] Raw scores on each test measure were converted to percentile scores with reference to the standardisation sample, and these were converted into five neuropsychologically meaningful grade scores as follows: grade 5, at or above the 50th percentile; grade 4, at or above the 25th percentile but below the 50th; grade 3, at or above the 5th percentile but below the 25th; grade 2, at or above the 1st percentile but below the 5th; grade 1, below the 1st percentile.

Two global measures of dementia were computed: first a composite cognitive score was obtained by summing the nine individual grade scores (with the exception of the NART score, which is little affected by dementia of Alzheimer's type [20]) and recording the mean of these grade scores; secondly a dementia index was obtained using the method of Nelson and O'Connell [30], by recording the discrepancy between an estimated pre-morbid IQ (from the NART IQ equivalent score) and the measured prorated full scale IQ. Raw scores were used to compare the groups on each of the individual tests.

Results

The mean scores and standard deviations for the two global measures of severity of dementia, the composite cognitive score and the dementia index score, for the SAD and FAD groups and the FAD PS–1 subset are given in Table 1. A non-parametric statistic was preferred since there was a skewed distribution of scores on some of the measures. The Mann-Whitney *U* test was computed, in this and in subsequent analyses, to compare the means of the SAD group with those the FAD group and the FAD PS–1 subset. The *Z* values of and the two-tailed probability levels are given in Table 1. There were no significant differences in any of the group comparisons, indicating that not only the SAD and FAD groups but also the smaller FAD PS–1 subset were very similar in terms of overall severity of dementia.

The mean scores and standard deviations for the individual test measures for each group are given in Table 2. Those of the original standardisation samples are also given to provide a baseline reference point. The Mann-Whitney *U* test was computed to compare the means of the SAD and FAD groups and those of the SAD group and FAD PS–1 sub-group (see Table 2). The FAD group scored significantly higher on two tests: the GNT and the VOSP Silhouettes test. The SAD group scored significantly higher on the WAIS Verbal IQ measure. Considering the performance of the smaller FAD PS–1 subset, an identical pattern of results was obtained. Of particular interest is the relative weakness of naming in the SAD group in the context of their rather better performance on the more general measure of language competence, the Verbal IQ of the WAIS-R.

The SAD group was significantly older than both the FAD group and the FAD PS–1 sub-set (t=5.3, $P < 0.001$, and t=4.5, $P < 0.001$, respectively). It should therefore be

Tab. 1 Global cognitive measures for each group (mean ±standard deviation) and group comparisons (*Z* and *P* values) (*SAD* sporadic Alzheimer's disease, *FAD* familial Alzheimer's disease, *FAD PS–1* familial Alzheimer's disease presenilin 1)

Measure	SAD (*n*=26)	FAD (*n*=24)	FAD PS–1 (*n*=13)	SAD vs FAD	SAD vs FAD PS–1
Composite cognitive score	2.58±0.96	2.4±0.70	2.5±0.80	*Z*=0.7, NS	*Z*=0.48, NS
Dementia index	22.2±16.7	23.6±14.0	24.1±13.8	*Z*=0.60 NS	*Z*=0.57, NS

Tab. 2 Individual test scores (Mean ±standard deviation) and group comparisons (*Z* and *P* values) (*SAD* sporadic Alzheimer's disease, *FAD* familial Alzheimer's disease, *FAD PS–1* familial Alzheimer's disease presenilin 1)

Test	Standardisation sample	SAD (*n*=26)	FAD (*n*=24)	FAD PS–1 (*n*=13)	SAD vs FAD	SAD vs FAD PS–1
Reading IQ equivalent	100±15	105.7±15.7	100.4±15.1	100.7±15.5	*Z*=1.27, NS	*Z*=1.01, NS
Verbal IQ	100±15–	86.9±15.5	79.5±10.0	79.4±12.2	*Z*=1.94, *P* < 0.05	*Z*=2.01, *P* < 0.05
Performance IQ	–100±15	80.3±18.6	75.0±10.5	76.5±13.3	*Z*=0.56, NS	*Z*=0.37, NS
Verbal memory RMT words (max. 50)	45.3±3.4	29.4±5.4	28.1±5.0	29.5±6.2	*Z*=0.83, NS	*Z*=0.02, NS
Visual memory: RMT faces (max. 50)	44.3±4.1	31.2±7.4	31.2±4.9	30.6±4.7	*Z*=0.32, NS	*Z*=0.38, NS
Naming: GNT (max. 30)	20.4±4.1	11.4±7.7	17.9±5.8	18.1±5.5	*Z*=2.80, *P* < 0.01	*Z*=2.51, *P* < 0.01
Spelling: GST (max. 30)	19.7±6.0	13.5±9.7	12.3±8.5	12.6±9.2	*Z*=0.36, NS	*Z*=0.11, NS
Arithmetic: GAT (max. 24)	12/24±11.9	3.5±3.7	4.1±5.2	4.6±6.4	*Z*=0.73, NS	*Z*=0.08, NS
Perception: Object-Silhouettes (max. 30)	23/30	13.5±6.3	18.3±5.2	19.1±6.2	*Z*=2.57, *P* < 0.01	*Z*=2.44, *P* < 0.02
Processing speed: number copying digit copy (s)	35±11.9	75.7±57.9	62.2±25.9	62.7±24.9	*Z*=0.325, NS	*Z*=0.45, NS

Tab. 3 Comparison of performance on verbal and non-verbal tests (*SAD* sporadic Alzheimer's disease, *FAD* familial Alzheimer's disease, *FAD PS–1* familial Alzheimer's disease presenilin 1)

	SAD	FAD	FAD PS–1
Verbal IQ vs Performance IQ	t=2.9, $P < 0.01$	t=2.9, $P < 0.01$	t=1.3, $P < 0.1$
Verbal memory vs Visual memory	t=1.5, NS	t=1.3, NS	t=1.54, NS

noted that in the SAD group performance on the naming task and the perceptual task was not correlated with age (Spearman's r=0.15, $P > 0.1$ and 0.19, $P > 0.1$, respectively). The Verbal IQ is an age corrected measure.

A further analysis to establish relative vulnerability compared performance on two pairs of tests, verbal with performance IQ and verbal memory with visual memory, using the grade scores. Related t tests were computed for the SAD and FAD groups and FAD PS–1 subset for each of these test pairs (see Table 3). The expected superiority of verbal IQ over performance IQ was observed in the FAD and SAD groups but there was only a weak trend in the FAD PS–1 subset. However, there was no suggestion of any selective vulnerability of verbal or visual memory in any of the patient groupings.

Discussion

The present findings provide some tentative evidence for a differential pattern of cognitive functioning in patients with FAD as compared with SAD. Specifically, the FAD group scored at a higher level on the tests of naming ability and of object perception than the SAD group. The converse pattern of performance was observed with the Verbal IQ measure. Although there was genetic heterogeneity within the FAD group as a whole, an identical pattern of results in the smaller subset of *PS–1* mutations was observed.

It has been suggested that differential patterns of performance in SAD and FAD may be accounted for by a failure to match for severity of dementia and a failure to take into account possible confounding effects of age differences. It is also important to achieve equivalence of task difficulty across each of the cognitive domains, otherwise spurious profiles of impairment and preservation may emerge.

We adopted two measures of severity of dementia. First, a composite score based on all the cognitive measures except reading, which has been shown to be relatively stable during the early phases of degenerative dementias. Secondly, following Nelson and O'Connell [30], we computed a dementia index by recording the discrepancy between a reading IQ equivalent, and the measured prorated full scale WAIS IQ. It should be noted that this procedure underestimates the dementia index in any individual with reading difficulties. In our study the SAD and FAD groups and the FAD PS–1 sub-set were all very similar on both these measures. Furthermore, the two groups were very similar in their performance on the memory tests used in this study. Consequently it is unlikely that the distinctive patterns of performance that we have observed should be attributed to differences in the severity of dementia.

All the tests in this battery were selected on the basis that they were graded in difficulty, such that scores were normally or nearly normally distributed in the original standardisation population, thus a 50th percentile score on each test can be assumed to be equivalent in terms of task difficulty. It is therefore valid to compare patterns of performance across tests. We would therefore argue that the distinctive pattern that contrasts a higher Verbal IQ in the SAD group and higher naming and perception scores in the FAD and FAD PS–1 subset cannot be attributed to a failure to equate for task difficulty.

It was not possible to identify a group of SAD patients with a sufficiently early age at onset to match the FAD group. However, the possibility that the relative preservation of naming skills in the FAD group and FAD PS–1 subset can be accounted for in terms of their relative younger age is unlikely. First, in normal subjects up to the age of 70 years there are no significant effects of age on performance on the GNT [23]. Secondly in the SAD group, the older group whose performance was relatively weak on the naming test, there was no correlation between age and naming ability. The finding of relative preservation of naming in the FAD group is strengthened by the finding that the verbal IQ of this group was lower than that in the SAD group. This double dissociation points to there being a specific and selective island of preservation in the FAD group. This pattern was clearly maintained in the smaller FAD PS–1 group.

There are very few data in the literature that anticipate our present findings. In one previous study Duara et al. [11] failed to find superior naming skills in a small autosomal dominant familial group, although naming was relatively preserved in a larger group of patients with a positive family history. In a longitudinal study of individuals known to be at risk of FAD, the ten who developed probable or possible FAD during the course of the study, when assessed at a very early stage in the disease process, still performed at the same normal level as the unaffected at risk subjects on tests of naming and perception [29]. In these same individuals a selective verbal memory deficit was an early feature. However, in the present study there was no evidence of a relative vulnerability of verbal memory in any group [31].

The pattern of relative preservation of naming and perceptual skills is also a feature of our larger group of FAD cases at a more advanced stage. This was not observed in the SAD group in whom naming and percep-

tual skills were quite significantly compromised. These different cognitive profiles might be accounted for by a greater degree of heterogeneity among the SAD group and a greater degree of homogeneity among the FAD group. In this context it is worth noting that, at least for the Verbal IQ measure and the GNT score, the standard deviations are larger in the SAD group than in the FAD group. Different sub-types of SAD are well recognised, for example, with a posterior presentation, impairment of perceptual skills would be an early feature or with a temporal presentation, impairment of naming skills would be prominent [32–34]. We suggest that the clinical presentation of FAD sparing naming and perception also presents a distinctive clinical subtype, which may have a distinctive anatomical substrate.

It is possible that further subtle differences in cognitive profiles will be observed between the *PS–1* mutations, although these could not be discerned with the small numbers of patients with each individual mutation. Nevertheless, it has been possible to demonstrate that within AD the underlying molecular pathology can be linked to clinical heterogeneity. The exact mechanism by which mutations in the *PS–1* gene leads to AD is still not established although the current evidence suggests an increase in the proportion of $A\beta_{1-42}$ as opposed to $A\beta_{1-40}$ [35, 36]. The former is more amyloidgenic thus driving the formation of senile plaques and subsequently neurofibrillary tangles. Thus although the final common pathway of plaque and tangle formation is the same, subtle but consistent clinical differences suggest selective vulnerability of neural systems to the primary disease process.

References

1. Swearer JM, O'Donnell B, Drachman DA, Woodward BM (1992) Neuropsychological features of familial Alzheimer's disease. Ann Neurol 32:687–694
2. Breitner JC, Folstein M (1984) Familial Alzheimer's disease; a prevalent disorder with specific clinical features. Psychol Med 14:63–80
3. Bird TD, Sumi SM, Nemens EJ, et al (1989) Phenotypic heterogeneity in Familial Alzheimer's disease: a study of 24 kindreds. Ann Neurol 25:12–21
4. Fox NC, Kennedy AM, Harvey RJ, et al (1997) Clinicopathological features of familial Alzheimer's disease associated with the M139 V mutation in the presenilin 1 gene. Pedigree but not mutation specific age at onset provides evidence for a further genetic factor. Brain 120:491–501
5. Kennedy AM, Newman SK, Frackowiak RSJ, et al (1995) Chromosome 14 linked familial Alzheimer's disease: a clinico-pathological study of a single pedigree. Brain 118:185–205
6. Cruts M, Van Broeckhoven C (1998) Presenilin mutations in Alzheimer's disease. Hum Mutat 113:190
7. Strittmatter WJ, Saunders AM, Schmechel D, et al (1993) Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 90:1977–1981
8. Mayeux R, Stern Y, Ottman R, et al (1993) The apolipoprotein epsilon 4 allele in patients with Alzheimer's disease. Ann Neurol 34:752–754
9. Lehtovirta M, Soininen H, Helisalmi S, et al (1996) Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: relation to apolipoprotein E polymorphism. Neurology 46:413–419
10. Knesevich J, Toro F, Morris J, laBarge E (1985) Aphasia, family history and the long course of senile dementia of the Alzheimer-type. Psychiatry Res 14:255–263
11. Duara R, Lopez AR, Barker WW, et al (1993) A comparison of familial and sporadic Alzheimer's disease. Neurology 43:1377–1384
12. Spinnler H, Della Sala S (1988) Role of clinical neuropsychology in the neurological diagnosis of Alzheimer's disease. J Neurol 235:259–271
13. Fox NC, Warrington EK, Freeborough PA, et al (1996) Presymptomatic hippocampal atrophy in Alzheimer's disease: a longitudinal MRI study. Brain 119:2001–2007
14. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's Disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–944
15. Goate A, Chartier Harlin M-C, Mullan M, et al (1991) Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 349:704–706
16. Chartier Harlin M-C, Crawford F, Houlden H, et al (1991) Early onset Alzheimer's disease caused by mutations at codon 717 of the beta amyloid precursor gene. Nature 353:844–846
17. Hutton M, Busfield F, Wragg M, et al (1996) Complete analysis of the presenilin 1 gene in early onset Alzheimer's disease. Neuroreport 7:801–805
18. Kennedy AM, Fox N, Seaward J, et al (1994) A neuroimaging study of individuals with app mutations. Neurology 44:299–299
19. Hachinski V, Lassen N, Marshall J (1974) Multi-infarct dementia. A cause of mental deterioration in the elderly. Lancet II:207–209
20. Nelson HE, Willison J (1991) The National Adult Reading Test (NART) manual. NFER-Nelson, Windsor
21. Warrington EK, James M, Maciejewski C (1986) The WAIS as a lateralizing and localizing diagnostic instrument: a study of 656 patients with unilateral cerebral lesions. Neuropsychologia 24:223–239
22. Warrington EK (1984) Manual for the Recognition Memory Test for words and faces. NFER-Nelson, Windsor
23. McKenna P, Warrington EK (1983). The Graded Naming Test. NFER-Nelson, Windsor
24. Warrington EK (1997) The Graded Naming Test: a restandardisation. Neuropsychol Rehabil 7:143–146
25. Jackson M, Warrington EK (1986) Arithmetic skills in patients with unilateral cerebral lesions. Cortex 22:611–620
26. Baxter DM, Warrington EK (1994) Measuring dysgraphia: a graded-difficulty spelling test. Behav Neurol 7:107–116
27. Warrington EK, James M (1991) The visual object and space perception battery. Thames Valley Test, Bury St. Edmunds
28. Willison JR, Warrington EK (1992) Cognitive retardation in a patient with preservation of psychomotor speed. Behav Neurol 5:113–116
29. Fox NC, Warrington EK, Seiffer AS, Agnew SK, Rossor MN (1998) Presymptomatic cognitive deficits in individuals

at risk of familial Alzheimer's disease. A longitudinal prospective study. Brain 121:1631–1639
30. Nelson HE, O'Connell A (1978) Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. Cortex 14:234–244
31. Newman SK, Warrington EK, Kennedy AM, Rossor MN (1994) The earliest cognitive change in a person with familial Alzheimers disease – presymptomatic neuropsychological features in a pedigree with familial Alzheimers disease confirmed at necropsy. J Neurol Neurosurg Psychiatry 57:967–972
32. Levine DN, Lee JM, Fisher CM (1993) The visual variant of Alzheimer's disease: a clinicopathologic case study. Neurology 43:305–313
33. Saffran EM, Fitzpatrick-De Salme EJ, Coslett HB (1992) Visual disturbances in dementia. In: Schwartz MF (ed) Modular deficits in Alzheimer-type dementia. MIT Press, Cambridge, pp 297–327
34. Greene JD, Patterson K, Xuereb J, Hodges JR (1996) Alzheimer disease and nonfluent progressive aphasia. Arch Neurol 53:1072–1078
35. Scheuner D, Eckman C, Jensen M, et al (1996) Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. Nat Med 2:864–870
36. Wolfe MS, Xia W, Ostaszewski BL, Diehl TS, Taylor Kimberly W, Selkoe DJ (1999) Two transmembrane aspartates in presenilin–1 required for presenilin endoproteolysis and gamma-secretase activity. Nature 398:513–517