The natural history of early-onset dementia: the Artemis Project - a cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001764
Article Type:	Research
Date Submitted by the Author:	03-Jul-2012
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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology
Keywords:	Dementia < NEUROLOGY, GENETICS, Neurology < INTERNAL MEDICINE

The natural history of early-onset dementia: the Artemis Project – a cohort study

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JULY 2012

Key words: early-onset dementia, Alzheimer's disease, natural history, fronto-temporal dementia

Abstract word count = 270 words

Text word count = 2189 words

References = 22

Tables = 3

Figures = 3

SUMMARY

Focus: To describe the natural history of early onset Alzheimer's disease (AD) and fronto-temporal dementia (FTD) in terms of changes in cognitive assessment and staging, medical history and survival.

Key message: The difference in survival in patients with AD and FTD in our cohort might relate to the development of one or more cerebrovascular risk factors in FTD patients.

Strengths and limitations: A longitudinal prospective cohort of patients with a good sample size and long duration of follow-up using brief robust clinical measures. Future studies will allow more comprehensive assessments of memory and executive functions.

ABSTRACT

Objectives: The natural history of early-onset Alzheimer's disease (AD) and fronto-temporal dementia (FTD) remains to be described in detail. We seek to describe the natural history of early onset AD and FTD in terms of changes in cognitive assessment and staging, medical history and survival.

Design: Case control.

Setting: Neurodegenerative disorders research clinic.

Participants: 155 consecutive patients with clinically confirmed sporadic early-onset AD or FTD at a neurodegenerative disorders research clinic in Subiaco, Western Australia (The Artemis Project).

Methods: A detailed history was recorded from the patients at baseline, including education, family history and previous medical history. Mini-mental state exam (MMSE), global deterioration scale (GDS) and total functional capacity (TFC) were determined at each visit from 1994 until 2011. Kaplan-Meier survival analysis was performed.

Results: Patients with FTD were more likely to have a family history of dementia (p=0·026), to develop at least one cerebrovascular risk factor (p=0·003), manifest depression (Fisher's exact p=0·007), and to die during the follow-up period (Pearson chi-square 8·97, p=0·003). Kaplan-Meier survival estimates revealed a highly significant difference in the proportion of patients surviving the follow-up period (log rank 7·25, p=0·007) with FTD patients experiencing poorer survival than those with AD. The mean MMSE and TFC were consistently lower in those with FTD compared with those with AD over a decade of follow-up; mean GDS were consistently higher in those with FTD over the follow-up period.

Conclusion: We believe that the difference in survival in patients with AD and FTD in our cohort might relate to the development of one or more cerebrovascular risk factors in FTD patients and the severity of the underlying pathology.

OBJECTIVES

It is estimated that 24.3 million people worldwide have dementia and this is expected to rise to 81·1 million people in 2040.[1] Alzheimer's disease (AD) is the leading cause of dementia, contributing to up to three-quarters of dementias.[2] Early-onset dementia is the onset of dementia in those aged 65 years and under, the most common causes being AD and fronto-temporal dementia (FTD).[3,4] Patients with early-onset AD often present to the clinic with defective episodic memory, while those with FTD are characterised by disturbances in speech and behaviour.[3] While progress has been made describing the natural history of AD and FTD in older adults, the natural history of early-onset AD and FTD remains to be more fully elucidated. We seek to describe the natural history of early onset AD and FTD in terms of changes in cognitive assessment and staging, medical history and survival.

METHODS

This study is a longitudinal prospective cohort analysis of a group of patients identified in a neurodegenerative disorders research clinic in Subiaco, Western Australia, from 1 January 1994 until 31 January 2011: The Artemis Project. The Artemis Project is an attempt to study the neurobiology of early onset dementia of all causes in Western Australia. Participants consisted of 155 patients with clinically confirmed sporadic early-onset Alzheimer's disease or fronto-temporal dementia, with onset prior to 65 years, who gave informed consent and attended the clinic on more than one occasion.

Patients with early onset AD were diagnosed using NINCDS-ADRA criteria and supported by structural and functional imaging (FDG PET) and neuropsychometry.[3,5,6] Patients were diagnosed with FTD using existing published criteria[7] and refined as new technology (such as FDG PET) became available[6] and at annual review using contemporary international guidelines.[3,8] With this approach, no patients have been excluded and our neuropathological sensitivity and specificity for the diagnosis of AD and FTD = 100%.

The FTD group comprised only of patients with the behavioural variant of FTD for uniformity of analysis; patients identified with semantic dementia (n=1), primary progressive aphasia (n=8) and motor neuron disease – FTD complex (n=2) were not included.

A detailed history was recorded from the patient at baseline, including education, family history, and previous medical history. This information was then corroborated with the spouse or primary carer, and the general practitioner. Additionally, during follow-up this information was updated if the patient characteristics changed; for example, if a patient developed cancer.

Age at onset was determined from self and carer/spouse report of the onset of symptoms. Education is defined as self-reported years of formal education. Family history is defined as a self-reported family history of dementia in first- and second-degree relatives. Cerebrovascular risk factors are hypertension, hypercholesterolaemia, increased girth, obesity, diabetes, smoking, excessive alcohol consumption, coronary heart disease and peripheral vascular disease, the measurement of these has been described elsewhere.[9] The presence of at least one of these risk factors was determined from self-report and medical notes. The presence of mental illness (depression or psychosis) or other co-morbidities was also determined through self-report, carer information and medical notes.

Mini mental state exam (MMSE) was performed at each visit as a measure of cognition.[10] Global Deterioration Scale (GDS) and Total Functional Capacity (TFC) staging were determined for each visit as markers of the severity of the dementia and abilities to perform acts of daily living.[11,12] The ratings were performed by the same trained team of cognitive assessors.

DNA screening was performed on our patients with an autosomal dominant pattern of inheritance – nucleotide changes in the coding sequences of the amyloid precursor protein (APP), progranulin gene, presenilin–1 and presenilin–2 genes, Tau and SIGMAR 1 gene were performed by direct sequencing of

polymerosechoid reaction (PCR) products derived from genomic DNA. Nucleotide sequence information from each PCR product was obtained from both strands and possible mutations were verified by an independent amplification of the PCR product and resequenced. ApoE genotypes were determined by restriction fragment polymorphism analysis of PCR amplified products. Individuals identified with presenilin–1 mutation (Q222H), progranulin mutations and SIGMAR 1 mutations are not included in this study and will be reported elsewhere.

Statistical analyses, including chi-square tests for difference in proportions, t-tests for difference in means, and Kaplan-Meier survival analysis, were performed using Stata VII. As the MMSE and other variables are not normally distributed, the t-test was not used and the Kolmorgorov-Smirnov test employed to test for differences in means. No assumptions were violated for the Log-Rank test, nor drawing of the Kaplan-Meier curves – this is a non-parametric method. The Proportional Hazard Model was not used, which expects the baseline hazards for the two groups to be proportional.

RESULTS

The cohort consists of 155 early-onset dementia patients (92 with AD, 63 with FTD) (Table 1). Fifty-eight patients died during the study (AD = 25; FTD = 32); there were no drop-outs as spouses, carers and families remained in communication with study staff – even if admitted into nursing homes. There was a slightly greater, though not significant, proportion of males in the AD group compared with the FTD group (Pearson chi-square 2·76, p=0·096). The mean age of onset was similar between diagnosis groups for males (56·46 years vs. 55·73 years, p=0·583) and females (56·24 years vs. 55·60 years, p=0·670). Both groups had an average 11 years of education (p=0·900). Patients with FTD were more likely to have a family history of dementia (p=0·026), at least one cerebrovascular risk factor (p=0·003), a history of major depression diagnosed using DSM-IV criteria and distinguishable from apathy commonly found in FTD (Fisher's exact p=0·007), and to die during the follow-up period (Pearson chi-square 8·97, p=0·003). The cerebrovascular risk factors revealed a preponderance of

diabetes, smoking and increased alcohol consumption in the patients with FTD (Table 2). Kaplan-Meier survival estimates revealed a highly significant difference in the proportion of patients surviving the follow-up period, as can be seen in Figure 1 (log rank 7·25, p=0·007). There was no effect of APOE ε4 allele on the natural history of early onset Alzheimer's disease.

The mean MMSE was consistently lower in those with FTD compared with those with AD over a decade of follow-up (Figure 3). At baseline the MMSE, TFC and GDS did not show any significant difference between AD and FTD, providing further evidence for a worse progression of early onset FTD in comparison to AD. The boxplot shows that spread of MMSE scores is more condensed in those with FTD compared with AD across follow-up time. Similar results were seen with TFC. A greater range of GDS scores were seen in FTD patients compared with AD patients at baseline; however, a more condensed range of scores was seen across follow-up time. Mean GDS was consistently higher in those with FTD over the follow-up period. Some of the boxplots are missing (eg, year 11 for EOAD and years 9 and 10 for FTD): this is because median value is 0, min=0, max=0 so there is no box; for year 12 there is no data, hence no box. The unusual distribution beyond 9 years is likely due to small sample size, which would also be affecting the boxplots. It is possible there is a survival effect; those few who survive to that point and with longer follow-up may have a slower disease progression. The boxplots may also be affected by a clustering of scores at zero.

The majority of patients had a GDS score of four at baseline with a mean 4·02 years of follow-up (Table 3).

A graph of the changes in MMSE and GDS in two patients with early onset AD is presented in Figure 3 to highlight the heterogeneity in natural history in individual patients which may be overlooked in a cohort analysis. Patient 1 has no cerebrovascular risk factors and remained cognitively stable for a period of eight years. Patient 2 progressed rapidly over a period of two years. He was hypertensive,

smoked and consumed excessive alcohol. The magnetic resonance imaging shows white matter hyperintensities and progressive atrophy over this time. We did not observe such wide variation between FTD patients. White matter hyperintensities were identified in 10 patients with early onset AD (10.9%) and no patients with AD had evidence of small or large vessel ischaemia – apart from patient 2 (Figure 3) there was no correlation in other patients with white matter hyperintensities, prognosis and survival. No patients with FTD had white matter hyperintensities or evidence of stroke (small and large vessel).

DISCUSSION

A greater proportion of patients with FTD had a family history of dementia compared with AD patients. This is a similar result to those reported by Pasquier and colleagues.[13] They found a family history of dementia to be similar between AD and FTD patients, but a family history of dementia or psychiatric disorder to be much greater in FTD patients.[13] We are currently investigating further the role of family history as a risk factor in early-onset AD and FTD.

The difference in depression between those with FTD and those with AD is a complex issue. It may be that those with a history of depression are more at risk of FTD, or that patients with FTD are more likely to develop depression.

We found a difference in the MMSE, GDS and TFC between AD and FTD patients during the progress of the study, but not at the commencement of the study. The greater decline in MMSE in FTD patients might be attributable to the more aggressive nature of the dementia in FTD: findings supported by the changes in the functional scales and the differences in survival.

We sought to describe the natural history of early-onset dementia, particularly AD and FTD. We found that survival is significantly reduced in those with FTD compared with those with AD, as seen by

Koedam and colleagues.[4] In contrast, Pasquier and colleagues found survival to be similar between patients with AD and FTD after controlling for sex, age, age at onset and education level, although they did find sudden death to be more frequent in FTD.[13] This differences may be related to the inclusion of older onset dementia patients in this study. There was approximately a decade difference in mean age between Pasquier's AD and FTD patients while mean average was the same in our population. We speculate that the difference in survival between AD and FTD in our cohort might relate to the greater presence of one or more cerebrovascular risk factors in FTD patients – an unexpected finding. While our previous research had identified hypertension to be a risk factor in the development of AD, it does not appear to affect survival. Other elements of cardiovascular risk including smoking, increased alcohol consumption and obesity may develop in FTD as part of the frontal disinhibition syndrome and these factors may impact on survival. We need to be mindful of the risk profile in individuals with early onset AD as management of cerebrovascular risk factors will affect progress (Figure 3).

Our experience of different rates of progression in AD appears to be similar to the results of Thalhauser and Komarova.[14] They used a different staging system, the functional assessment staging (FAST) procedure and found that if a patient progressed rapidly through a FAST stage he or she was likely to experience rapid progression through the remaining stages (similar to the patient described in Figure 3). It has been found that comorbidity can be associated with an increased disease progression,[15] and this reflects our experiences with patients like Patient 2 (Figure 3). Additionally, poor physical health in those with AD is linked to poorer survival.[16] Work by Paradise and colleagues modelled survival time from age, constructional and gait apraxia in a much older cohort (mean age 81 years). These patients experienced shorter survival (approximately three years), likely due to the age of the population studied, whilst others found a median survival of 6.7 years in a younger group of AD patients aged 60-69 years.[17,18] While determining the predictors of survival in older age groups, Wolfson and colleagues were unable to determine the estimated probability of survival in early-onset AD after adjustment for rapid progression (length bias) because of a small early-onset sample size.[19]

Rapid versus slow progression may be related to structural and functional changes in the brain. Kim and colleagues suggested that a greater degree of glucose hypometabolism in the brain at the same level of dementia severity in early-onset versus late-onset AD patients might reflect rapid disease progression.[20] Sluimer identified that more generalised whole-brain atrophy may reflect rapid disease progression in comparison with more localised hippocampal atrophy in slow progressing AD;[21] Karas suggested the precuneus as a marker for progression of early-onset AD.[22]

CONCLUSION

In conclusion we have described the natural history of early onset AD and FTD, and observed that patients with FTD progress faster than those with AD: a finding which might relate to the development of cerebrovascular risk factors during the course of the illness and differences in aggression of the underlying pathology.

AUTHORS' CONTRIBUTIONS

ERA helped collect and collate data; analyzed data; and helped draft the manuscript.

MKB helped analyze data and performed the statistical analyses.

PKP collected data; collated and analyzed data; and helped draft the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

FUNDING

This project was funded by York Neuroscience Discovery Inc.

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Table 1: Patient characteristics

Characteristic	AD (n=92)	FTD (n=63)
Sex, male, n (%)	43 (53·35)	38(46·91)
Age at onset, mean (std dev) - male - female	 56·46 (5·84) 56·24 (5.99)	 55·73 (6·04) 55·60 (6.42)
Education, years, mean (std dev)	11·08 (3·30)	11·01 (2·96)
Family history of dementia, n (%)	15 (16·48)	20 (31·75)[a]
Cerebrovascular risk factors present, n (%)	20 (21·98)	28 (44·44)[b]
Depression, n (%)	10 (10·99)	14 (22·22)[b]
Cancer, n (%)	2 (2·17)	3 (4·76)
MMSE, mean SD	21 (7)	21(7)
TFC, mean SD	8·7 (2·6)	7·2 (2·7)
GDS, mean SD	3·3 (1·1)	3·9 (1·1)
Deceased, n (%)	25 (27·17)	32 (50·79)[b]

a: p-value <0.05; b: p-value<0.01

Table 2: Cerebrovascular risk factors in early onset dementia

Risk factor	AD (n=92)	FTD (n=63)
Hypertension	16	7
High cholesterol	11	12
Increased girth	11	14
Obesity	8	10
Diabetes	3	8
Current smoker	5	14
Moderate or excessive alcohol consumption	5	13
Coronary heart disease	9	4
Peripheral vascular disease	2	1

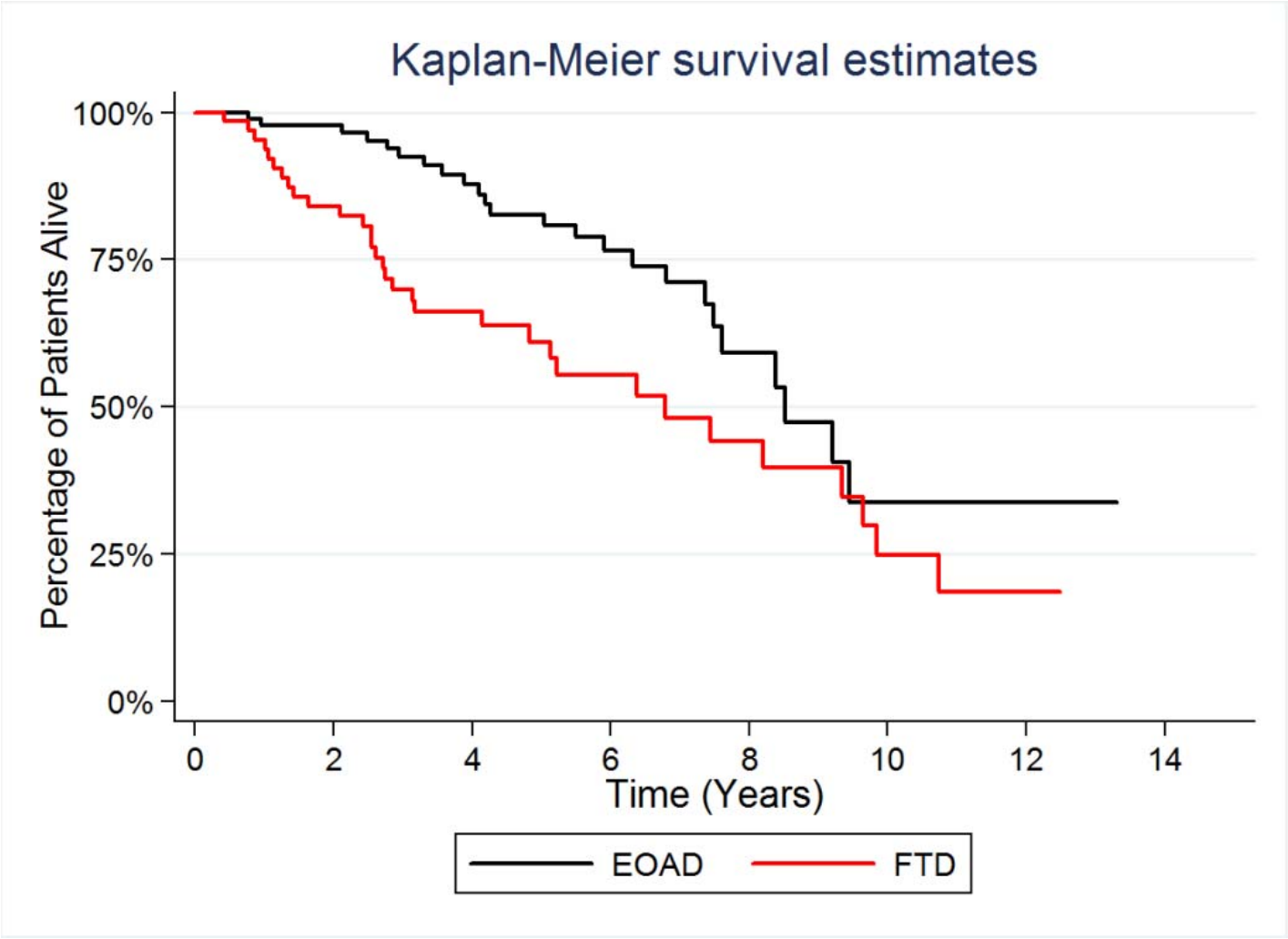
Table 3: Mean follow-up in years by baseline GDS score

GDS stage at baseline	n	Years of follow-up, mean (std dev)
1	6	7·70 (3·88)
2	20	4·40 (1·98)
3	43	3·15 (2·27)
4	62	4·02 (3·09)
5	21	2·22 (2·48)
6	2	0·74 (0·42)
7	1	0·82 (-)

Figure 1: Survival analysis of early-onset AD and FTD patients in time (years) from baseline visit

Figure 2: Boxplot and line graphs showing the change in distribution and mean MMSE, GDS, and TFC score over time. Note the large variation in score from nine years onward is the result of a small sample size at those time-points.

Figure 3: Changes in MMSE and GDS score in two patients with early-onset AD. Patient 1 experienced a rapid deterioration, whilst patient 2 experienced slower disease progression (both patients were APOE ε4 homozygous). Patient 1 had no cerebrovascular risk factors. Patient 2 had poorly controlled hypertension, smoked and consumed excessive alcohol. His MRI revealed progressive atrophy and increase in white matter hyperintensities (A = baseline; B = 24 months).



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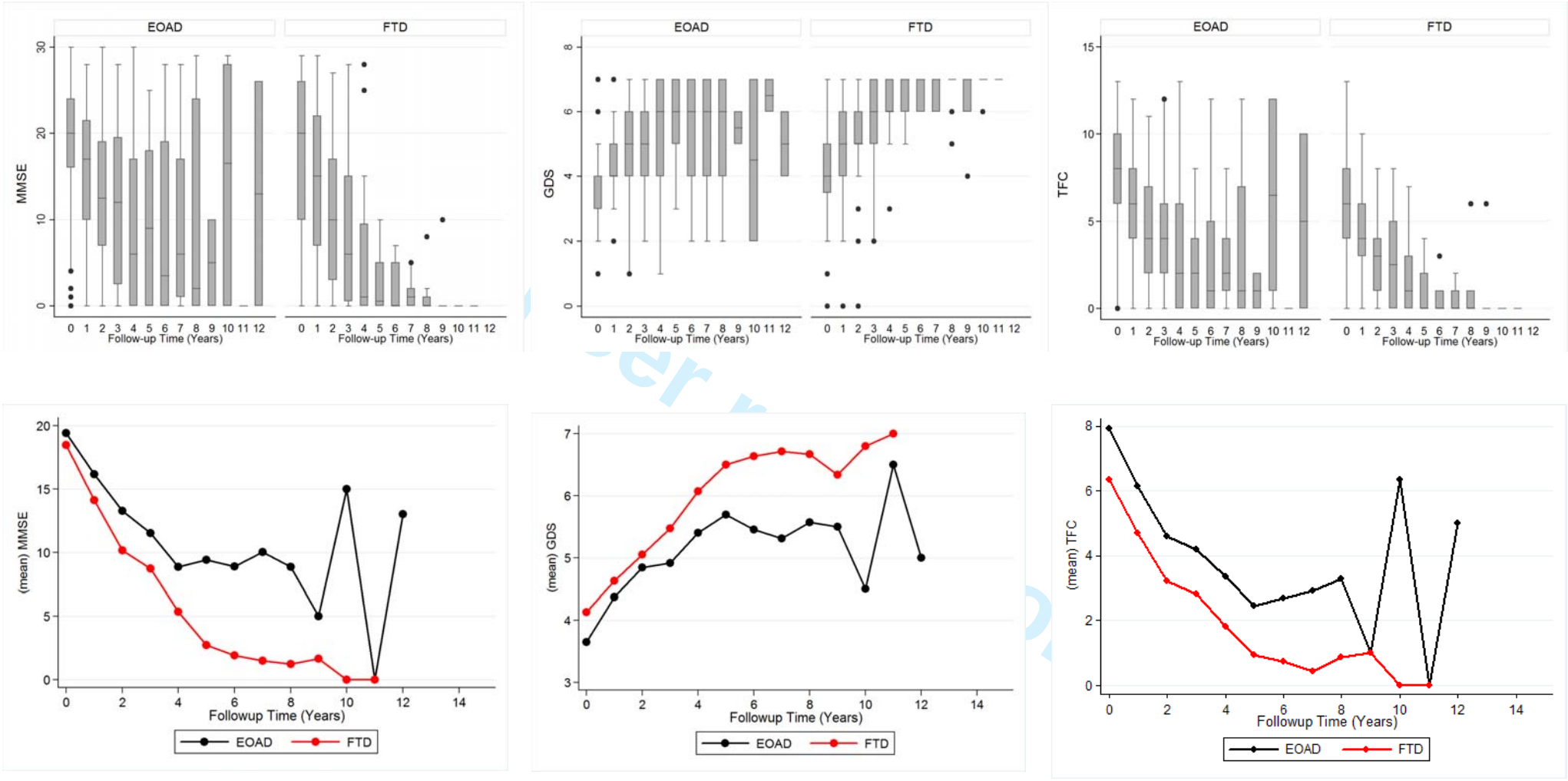
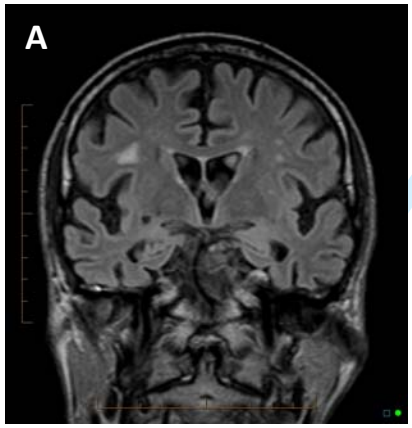
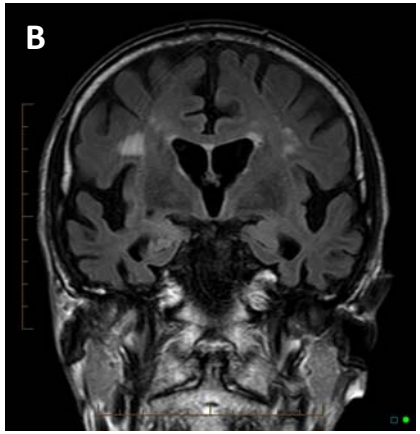
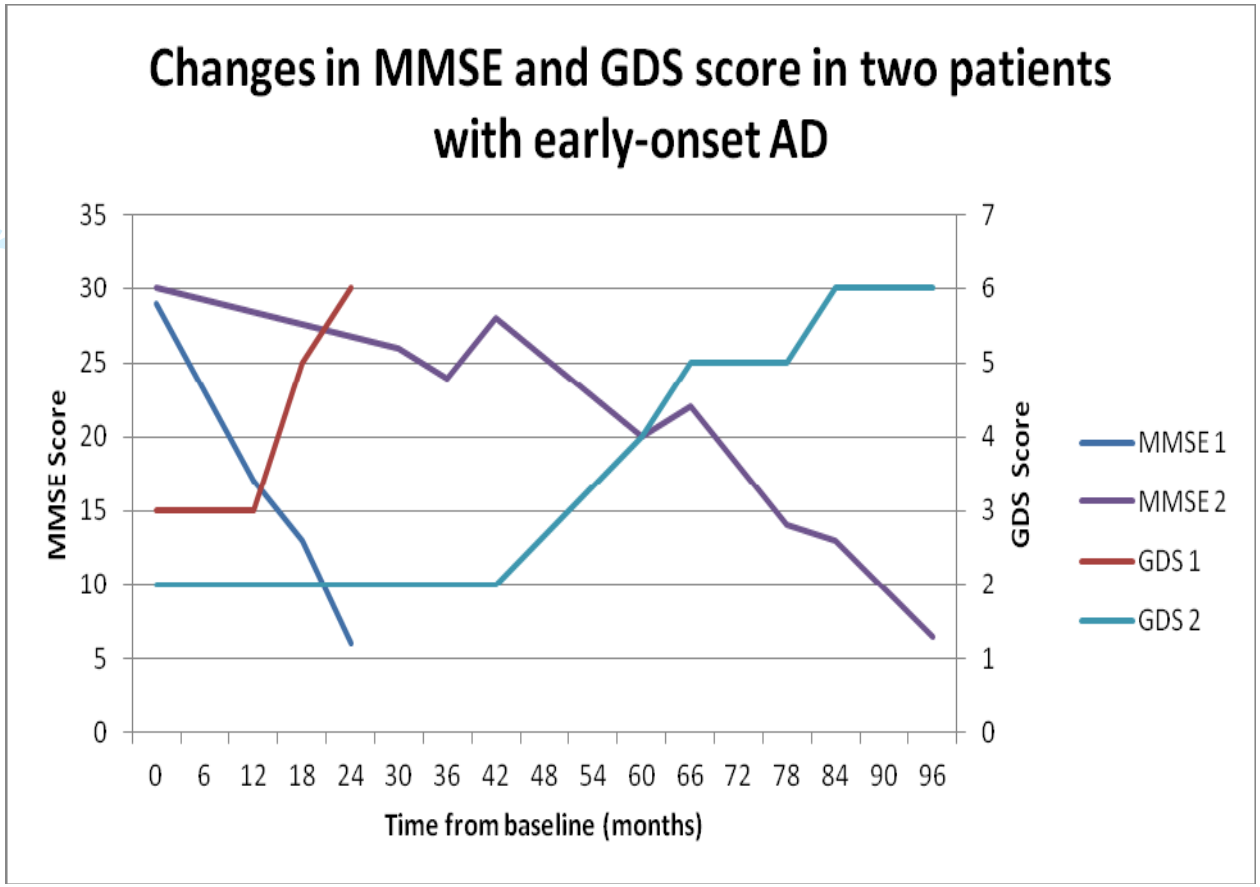


Figure 2: Boxplot and line graphs showing the change in distribution and mean MMSE, GDS, and TFC score over time. Note the large variation in score from nine years onward is the result of a small sample size at those time-points.







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RESPONSE TO REVIEWERS

Reviewer 1

Comment:

The authors mentioned that diagnosis was made according to current international guidelines and included imaging. This retrospective application of clinical guidelines might be inconsistent with prospective cohort analysis. Moreover, it is unclear how to make a clinical diagnosis of FTD. If that was made based on clinical diagnostic criteria of FTD (Neary et al. Neurology 1998), some patients should be excluded in this study. Because FTLD has clinical subtypes including behavioral variant, semantic dementia, and progressive aphasia, it should be described which subtype was examined.

Response:

This has been addressed in last paragraph of page 4 and first paragraph of page 5.

Comment:

The presence or absence of cerebrovascular risk factors depends on one or more risk factors, indicating the wide range of risk factors in each patient. Because the authors concluded that cerebrovascular risk factors contribute to poorer survival, they should describe the details of risk factors, including the frequency of each disease. Moreover, it would be helpful to mention cerebrovascular disease (CVD) on MRI image between AD and FTD. Whether the presence or absence of CVD contribute to survival might be important in both disorders.

Response:

Refer first para of 'Results' section and accompanying Table 2.

Reviewer 2

Comment:

1) I suppose that the baseline cohort was composed of 155 patients, it would be interesting to know the cohort size at the end of the Study, most patients died but I guess that some patients dropped out (how many? Why?)

Response:

Described in second sentence of 'Results' section.

Comment:

2) The Authors should add they took DNA samples from the patients in the Method section since they report data on APO polymorphism in Results section. What about mendelian forms of AD and FTD in their cohort? Were they screened? The Authors report that they included sporadic forms, nevertheless then they find a positive family history in many patients. Since the cohort is composed of patients with early-onset dementia I would guess a number of mendelian forms.

Response:

DNA screening has been discussed under 'Methods' in the paragraph commencing at the end of page 5.

Comment:

3) In Table 1 the Authors report data on depression: what do they mean for depression, major depression or what else? how it was diagnosed?

Response:

Refer to paragraph 1 of 'Results' section: "a history of major depression diagnosed using DSM-IV criteria and distinguishable from apathy commonly found in FTD".

Comment:

4) I suggest to report baseline MMSE score of the two groups in Table 1 (with the possible significance level if there was difference between the two groups). I would suppose that at disease onset MMSE score was less impaired in FTD patients as compared to AD patients, if

there was no difference, this finding should be discussed thus representing a possible further evidence for a worse progression of early-onset FTD vs early-onset AD.

Response:

This has been addressed in 2nd sentence of 2nd paragraph of 'Results' section.

Comment:

5) Figure 2 shows a weird distribution: how do the Authors explain the peak on MMSE and TFC (and consequent GDS reduction) at the 10th and 12th year for EOAD? Furthermore some boxplots are missing (11th year for EOAD, 9th year, 10th year etc for FTD).

Response:

This has been addressed at end of 2nd paragraph of 'Results' section.

Comment:

6) The relationship between depression and apathy is quite complex, how the Authors can exclude that diagnosis of depression in FTD patients was not biased by apathy symptoms which are very common in FTD? The Authors should better detail the possible contribution of apathy in determining depressive syndrome, otherwise their conclusions on the relation between depression and FTD could be hasty.

Response:

Patients with FTD were more likely to have a history of major depression diagnosed using DSM-IV criteria and distinguishable from apathy commonly found in FTD (refer 1st paragraph of 'Results' section).

Reviewer 3

Comment:

I could not find in the Methods or Results sections a statement informing if the statistical analyses (e.g. t-tests for difference in means, Kaplan-Meier survival analysis) assumptions have been met and if some participants were dropped in relation to the baseline.

Response:

This has been discussed in the last paragraph of the 'Methods' section.

BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001764.R1
Article Type:	Research
Date Submitted by the Author:	13-Aug-2012
Complete List of Authors:	Atkins, Emily; Neurodegenerative Disorders Research Pty Ltd, Bulsara, Max; University of Notre Dame, Biostatistics Panegyres, Peter; Neurodegenerative Disorders Research Pty Ltd,
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Mental health
Keywords:	Dementia < NEUROLOGY, GENETICS, Neurology < INTERNAL MEDICINE

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REVISED - AUGUST 2012

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Key message: The difference in survival in patients with AD and FTD in our cohort might relate to the development of one or more cerebrovascular risk factors in FTD patients.

Strengths and limitations: A longitudinal prospective cohort of patients with a good sample size and long duration of follow-up using brief robust clinical measures. The limitations of this study are that the investigation was performed at a single study centre and more comprehensive assessments of memory and executive functions need to be performed in future studies.

ABSTRACT

Objectives: The natural history of early-onset Alzheimer's disease (AD) and fronto-temporal dementia (FTD) remains to be described in detail. We seek to describe the natural history of early onset AD and FTD in terms of changes in cognitive assessment and staging, medical history and survival.

Design: Longitudinal prospective cohort analysis.

Setting: Neurodegenerative disorders research clinic.

Participants: 155 consecutive patients with clinically confirmed sporadic early-onset AD or FTD at a neurodegenerative disorders research clinic in Subiaco, Western Australia (The Artemis Project).

Methods: A detailed history was recorded from the patients at baseline, including education, family history and previous medical history. Mini-mental state exam (MMSE), global deterioration scale (GDS) and total functional capacity (TFC) were determined at each visit from 1994 until 2011. Kaplan-Meier survival analysis was performed.

Results: Patients with FTD were more likely to have a family history of dementia (p=0·026), to develop at least one cerebrovascular risk factor (p=0·003), manifest depression (Fisher's exact p=0·007), and to die during the follow-up period (Pearson chi-square 8·97, p=0·003). Kaplan-Meier survival estimates revealed a highly significant difference in the proportion of patients surviving the follow-up period (log rank 7·25, p=0·007) with FTD patients experiencing poorer survival than those with AD. The mean MMSE and TFC were consistently lower in those with FTD compared with those with AD over a decade of follow-up; mean GDS were consistently higher in those with FTD over the follow-up period.

Conclusion: We believe that the difference in survival in patients with AD and FTD in our cohort might relate to the development of one or more cerebrovascular risk factors in FTD patients and the severity of the underlying pathology.

OBJECTIVES

It is estimated that 24.3 million people worldwide have dementia and this is expected to rise to 81·1 million people in 2040.[1] Alzheimer's disease (AD) is the leading cause of dementia, contributing to up to three-quarters of dementias.[2] Early-onset dementia is the onset of dementia in those aged 65 years and under, the most common causes being AD and fronto-temporal dementia (FTD).[3,4] Patients with early-onset AD often present to the clinic with defective episodic memory, while those with FTD are characterised by disturbances in speech and behaviour.[3] While progress has been made describing the natural history of AD and FTD in older adults, the natural history of early-onset AD and FTD remains to be more fully elucidated. We seek to describe the natural history of early onset AD and FTD in terms of changes in cognitive assessment and staging, medical history and survival.

METHODS

This study is a longitudinal prospective cohort analysis of a group of patients identified in a neurodegenerative disorders research clinic in Subiaco, Western Australia, from 1 January 1994 until 31 January 2011: The Artemis Project. The Artemis Project is an attempt to study the neurobiology of early onset dementia of all causes in Western Australia. Participants consisted of 155 patients with clinically confirmed sporadic early-onset Alzheimer's disease or fronto-temporal dementia, with onset prior to 65 years, who gave informed consent and attended the clinic on more than one occasion.

Patients with early onset AD were diagnosed using NINCDS-ADRA criteria and supported by structural and functional imaging (FDG PET) and neuropsychometry.[3,5,6] Patients were diagnosed with FTD using existing published criteria[7] and refined as new technology (such as FDG PET) became available[6] and at annual review using contemporary international guidelines.[3,8] With this approach, no patients have been excluded and our neuropathological sensitivity and specificity for the diagnosis of AD and FTD = 100%.

The FTD group comprised only of patients with the behavioural variant of FTD for uniformity of analysis; patients identified with semantic dementia (n=1), primary progressive aphasia (n=8) and motor neuron disease – FTD complex (n=2) were not included.

A detailed history was recorded from the patient at baseline, including education, family history, and previous medical history. This information was then corroborated with the spouse or primary carer, and the general practitioner. Additionally, during follow-up this information was updated if the patient characteristics changed; for example, if a patient developed cancer.

Age at onset was determined from self and carer/spouse report of the onset of symptoms. Education is defined as self-reported years of formal education. Family history is defined as a self-reported family history of dementia in first- and second-degree relatives. Cerebrovascular risk factors are hypertension, hypercholesterolaemia, increased girth, obesity, diabetes, smoking, excessive alcohol consumption, coronary heart disease and peripheral vascular disease, the measurement of these has been described elsewhere.[9] The presence of at least one of these risk factors was determined from self-report and medical notes. The presence of mental illness (depression or psychosis) or other co-morbidities was also determined through self-report, carer information and medical notes.

Mini mental state exam (MMSE) was performed at each visit as a measure of cognition.[10] Global Deterioration Scale (GDS) and Total Functional Capacity (TFC) staging were determined for each visit as markers of the severity of the dementia and abilities to perform acts of daily living.[11,12] The ratings were performed by the same trained team of cognitive assessors.

DNA screening was performed on our patients with an autosomal dominant pattern of inheritance – nucleotide changes in the coding sequences of the amyloid precursor protein (APP), progranulin gene, presenilin–1 and presenilin–2 genes, Tau and SIGMAR 1 gene were performed by direct sequencing of

polymerosechoid reaction (PCR) products derived from genomic DNA. Nucleotide sequence information from each PCR product was obtained from both strands and possible mutations were verified by an independent amplification of the PCR product and resequenced. ApoE genotypes were determined by restriction fragment polymorphism analysis of PCR amplified products. Individuals identified with presenilin–1 mutation (Q222H), progranulin mutations and SIGMAR 1 mutations are not included in this study and will be reported elsewhere.

Statistical analyses, including chi-square tests for difference in proportions, t-tests for difference in means, and Kaplan-Meier survival analysis, were performed using Stata VII. As the MMSE and other variables are not normally distributed, the t-test was not used and the Kolmorgorov-Smirnov test employed to test for differences in means. No assumptions were violated for the Log-Rank test, nor drawing of the Kaplan-Meier curves – this is a non-parametric method. The Proportional Hazard Model was not used, which expects the baseline hazards for the two groups to be proportional.

RESULTS

The cohort consists of 155 early-onset dementia patients (92 with AD, 63 with FTD) (Table 1). Fifty-eight patients died during the study (AD = 25; FTD = 32); there were no drop-outs as spouses, carers and families remained in communication with study staff – even if admitted into nursing homes. There was a slightly greater, though not significant, proportion of males in the AD group compared with the FTD group (Pearson chi-square 2·76, p=0·096). The mean age of onset was similar between diagnosis groups for males (56·46 years vs. 55·73 years, p=0·583) and females (56·24 years vs. 55·60 years, p=0·670). Both groups had an average 11 years of education (p=0·900). Patients with FTD were more likely to have a family history of dementia (p=0·026), at least one cerebrovascular risk factor (p=0·003), a history of major depression diagnosed using DSM-IV criteria and distinguishable from apathy commonly found in FTD (Fisher's exact p=0·007), and to die during the follow-up period (Pearson chi-square 8·97, p=0·003). The cerebrovascular risk factors revealed a preponderance of

diabetes, smoking and increased alcohol consumption in the patients with FTD (Table 2). Kaplan-Meier survival estimates revealed a highly significant difference in the proportion of patients surviving the follow-up period, as can be seen in Figure 1 (log rank 7·25, p=0·007). There was no effect of APOE ε4 allele on the natural history of early onset Alzheimer's disease.

The mean MMSE was consistently lower in those with FTD compared with those with AD over a decade of follow-up (Figure 3). At baseline the MMSE, TFC and GDS did not show any significant difference between AD and FTD, providing further evidence for a worse progression of early onset FTD in comparison to AD. The boxplot shows that spread of MMSE scores is more condensed in those with FTD compared with AD across follow-up time. Similar results were seen with TFC. A greater range of GDS scores were seen in FTD patients compared with AD patients at baseline; however, a more condensed range of scores was seen across follow-up time. Mean GDS was consistently higher in those with FTD over the follow-up period. Some of the boxplots are missing (eg, year 11 for EOAD and years 9 and 10 for FTD): this is because median value is 0, min=0, max=0 so there is no box; for year 12 there is no data, hence no box. The unusual distribution beyond 9 years is likely due to small sample size, which would also be affecting the boxplots. It is possible there is a survival effect; those few who survive to that point and with longer follow-up may have a slower disease progression. The boxplots may also be affected by a clustering of scores at zero.

The majority of patients had a GDS score of four at baseline with a mean 4·02 years of follow-up (Table 3).

A graph of the changes in MMSE and GDS in two patients with early onset AD is presented in Figure 3 to highlight the heterogeneity in natural history in individual patients which may be overlooked in a cohort analysis. Patient 1 has no cerebrovascular risk factors and remained cognitively stable for a period of eight years. Patient 2 progressed rapidly over a period of two years. He was hypertensive,

smoked and consumed excessive alcohol. The magnetic resonance imaging shows white matter hyperintensities and progressive atrophy over this time. We did not observe such wide variation between FTD patients. White matter hyperintensities were identified in 10 patients with early onset AD (10.9%) and no patients with AD had evidence of small or large vessel ischaemia – apart from patient 2 (Figure 3) there was no correlation in other patients with white matter hyperintensities, prognosis and survival. No patients with FTD had white matter hyperintensities or evidence of stroke (small and large vessel).

DISCUSSION

A greater proportion of patients with FTD had a family history of dementia compared with AD patients. This is a similar result to those reported by Pasquier and colleagues.[13] They found a family history of dementia to be similar between AD and FTD patients, but a family history of dementia or psychiatric disorder to be much greater in FTD patients.[13] We are currently investigating further the role of family history as a risk factor in early-onset AD and FTD.

The difference in depression between those with FTD and those with AD is a complex issue. It may be that those with a history of depression are more at risk of FTD, or that patients with FTD are more likely to develop depression.

We found a difference in the MMSE, GDS and TFC between AD and FTD patients during the progress of the study, but not at the commencement of the study. The greater decline in MMSE in FTD patients might be attributable to the more aggressive nature of the dementia in FTD: findings supported by the changes in the functional scales and the differences in survival.

We sought to describe the natural history of early-onset dementia, particularly AD and FTD. We found that survival is significantly reduced in those with FTD compared with those with AD, as seen by

Koedam and colleagues.[4] In contrast, Pasquier and colleagues found survival to be similar between patients with AD and FTD after controlling for sex, age, age at onset and education level, although they did find sudden death to be more frequent in FTD.[13] This differences may be related to the inclusion of older onset dementia patients in this study. There was approximately a decade difference in mean age between Pasquier's AD and FTD patients while mean average was the same in our population. We speculate that the difference in survival between AD and FTD in our cohort might relate to the greater presence of one or more cerebrovascular risk factors in FTD patients – an unexpected finding. While our previous research had identified hypertension to be a risk factor in the development of AD, it does not appear to affect survival. Other elements of cardiovascular risk including smoking, increased alcohol consumption and obesity may develop in FTD as part of the frontal disinhibition syndrome and these factors may impact on survival. We need to be mindful of the risk profile in individuals with early onset AD as management of cerebrovascular risk factors will affect progress (Figure 3).

Our experience of different rates of progression in AD appears to be similar to the results of Thalhauser and Komarova.[14] They used a different staging system, the functional assessment staging (FAST) procedure and found that if a patient progressed rapidly through a FAST stage he or she was likely to experience rapid progression through the remaining stages (similar to the patient described in Figure 3). It has been found that comorbidity can be associated with an increased disease progression,[15] and this reflects our experiences with patients like Patient 2 (Figure 3). Additionally, poor physical health in those with AD is linked to poorer survival.[16] Work by Paradise and colleagues modelled survival time from age, constructional and gait apraxia in a much older cohort (mean age 81 years). These patients experienced shorter survival (approximately three years), likely due to the age of the population studied, whilst others found a median survival of 6.7 years in a younger group of AD patients aged 60-69 years.[17,18] While determining the predictors of survival in older age groups, Wolfson and colleagues were unable to determine the estimated probability of survival in early-onset AD after adjustment for rapid progression (length bias) because of a small early-onset sample size.[19]

Rapid versus slow progression may be related to structural and functional changes in the brain. Kim and colleagues suggested that a greater degree of glucose hypometabolism in the brain at the same level of dementia severity in early-onset versus late-onset AD patients might reflect rapid disease progression.[20] Sluimer identified that more generalised whole-brain atrophy may reflect rapid disease progression in comparison with more localised hippocampal atrophy in slow progressing AD;[21] Karas suggested the precuneus as a marker for progression of early-onset AD.[22]

The major limitations of this study are the measures used to follow patients and future studies will benefit from a more comprehensive memory assessment and more sophisticated measures of frontal lobe functions. Multicentre studies with larger numbers of patients will help to elucidate further the natural history of early onset dementia.

CONCLUSION

In conclusion we have described the natural history of early onset AD and FTD, and observed that patients with FTD progress faster than those with AD: a finding which might relate to the development of cerebrovascular risk factors during the course of the illness and differences in aggression of the underlying pathology. Larger multicentre studies with neuropathological confirmation are necessary to confirm these findings.

AUTHORS' CONTRIBUTIONS

ERA helped collect and collate data; analyzed data; and wrote the manuscript.

MKB helped analyze data; performed the statistical analyses; and helped draft the manuscript.

PKP collected data; collated and analyzed data; and wrote the manuscript.

CONFLICTS OF INTEREST

York Neuroscience Discover Inc (YND) is a charitable organisation operating under Australian law as a fundraising gift recipient that supports the research of Neurodegenerative Disorders Research Pty Ltd (NDR), a not-for-profit organisation devoted to the understanding of neurodegenerative disorders in young adults. YND is a tax deductible gift recipient governed by rules of association and a committee of management (ABN: 89 852 108 912). PKP is the Director of both NDR and YND; ERA is a Research Assistant of NDR.

FUNDING

This project was funded by York Neuroscience Discovery Inc (YND), the support organisation of Neurodegenerative Disorders Research Pty Ltd (NDR). While PKP and ERA are members of both YND and NDR, YND was not involved in the conduct of the study, data interpretation or decision to publish. YND solely provided the financial support for this project."

Data Sharing Statement

There is no additional data.

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Table 1: Patient characteristics

Characteristic	AD (n=92)	FTD (n=63)
Sex, male, n (%)	43 (53·35)	38(46·91)
Age at onset, mean (std dev) - male - female	 56·46 (5·84) 56·24 (5.99)	 55·73 (6·04) 55·60 (6.42)
Education, years, mean (std dev)	11·08 (3·30)	11·01 (2·96)
Family history of dementia, n (%)	15 (16·48)	20 (31·75)[a]
Cerebrovascular risk factors present, n (%)	20 (21·98)	28 (44·44)[b]
Depression, n (%)	10 (10·99)	14 (22·22)[b]
Cancer, n (%)	2 (2·17)	3 (4·76)
MMSE, mean SD	21 (7)	21(7)
TFC, mean SD	8·7 (2·6)	7·2 (2·7)
GDS, mean SD	3·3 (1·1)	3·9 (1·1)
Deceased, n (%)	25 (27·17)	32 (50·79)[b]

a: p-value <0.05; b: p-value<0.01

Table 2: Cerebrovascular risk factors in early onset dementia

Risk factor	AD (n=92)	FTD (n=63)
Hypertension	16	7
High cholesterol	11	12
Increased girth	11	14
Obesity	8	10
Diabetes	3	8
Current smoker	5	14
Moderate or excessive alcohol consumption	5	13
Coronary heart disease	9	4
Peripheral vascular disease	2	1

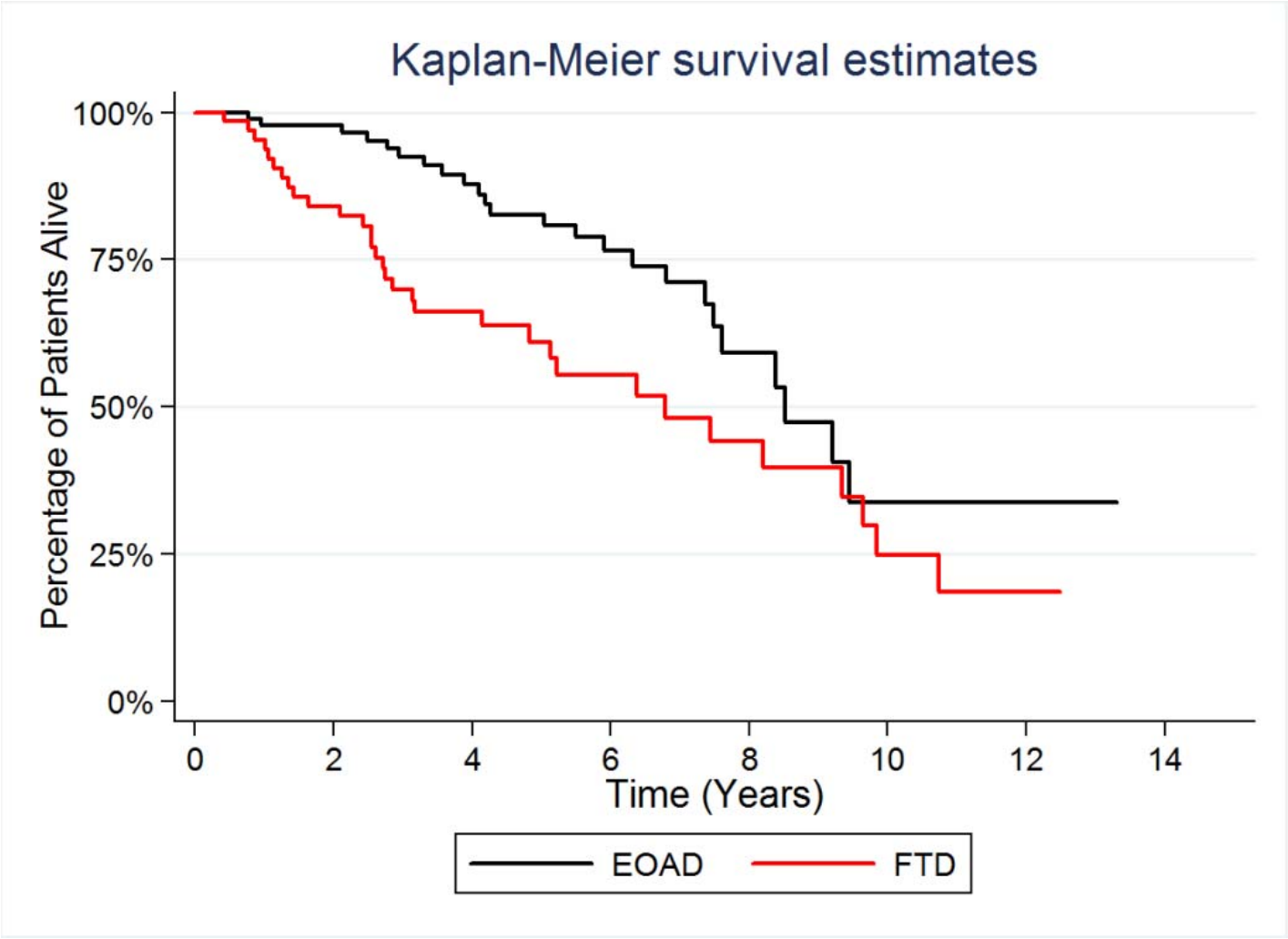
Table 3: Mean follow-up in years by baseline GDS score

GDS stage at baseline	n	Years of follow-up, mean (std dev)
1	6	7·70 (3·88)
2	20	4·40 (1·98)
3	43	3·15 (2·27)
4	62	4·02 (3·09)
5	21	2·22 (2·48)
6	2	0·74 (0·42)
7	1	0·82 (-)

Figure 1: Survival analysis of early-onset AD and FTD patients in time (years) from baseline visit

Figure 2: Boxplot and line graphs showing the change in distribution and mean MMSE, GDS, and TFC score over time. Note the large variation in score from nine years onward is the result of a small sample size at those time-points.

Figure 3: Changes in MMSE and GDS score in two patients with early-onset AD. Patient 1 experienced a rapid deterioration, whilst patient 2 experienced slower disease progression (both patients were APOE ε4 homozygous). Patient 1 had no cerebrovascular risk factors. Patient 2 had poorly controlled hypertension, smoked and consumed excessive alcohol. His MRI revealed progressive atrophy and increase in white matter hyperintensities (A = baseline; B = 24 months).



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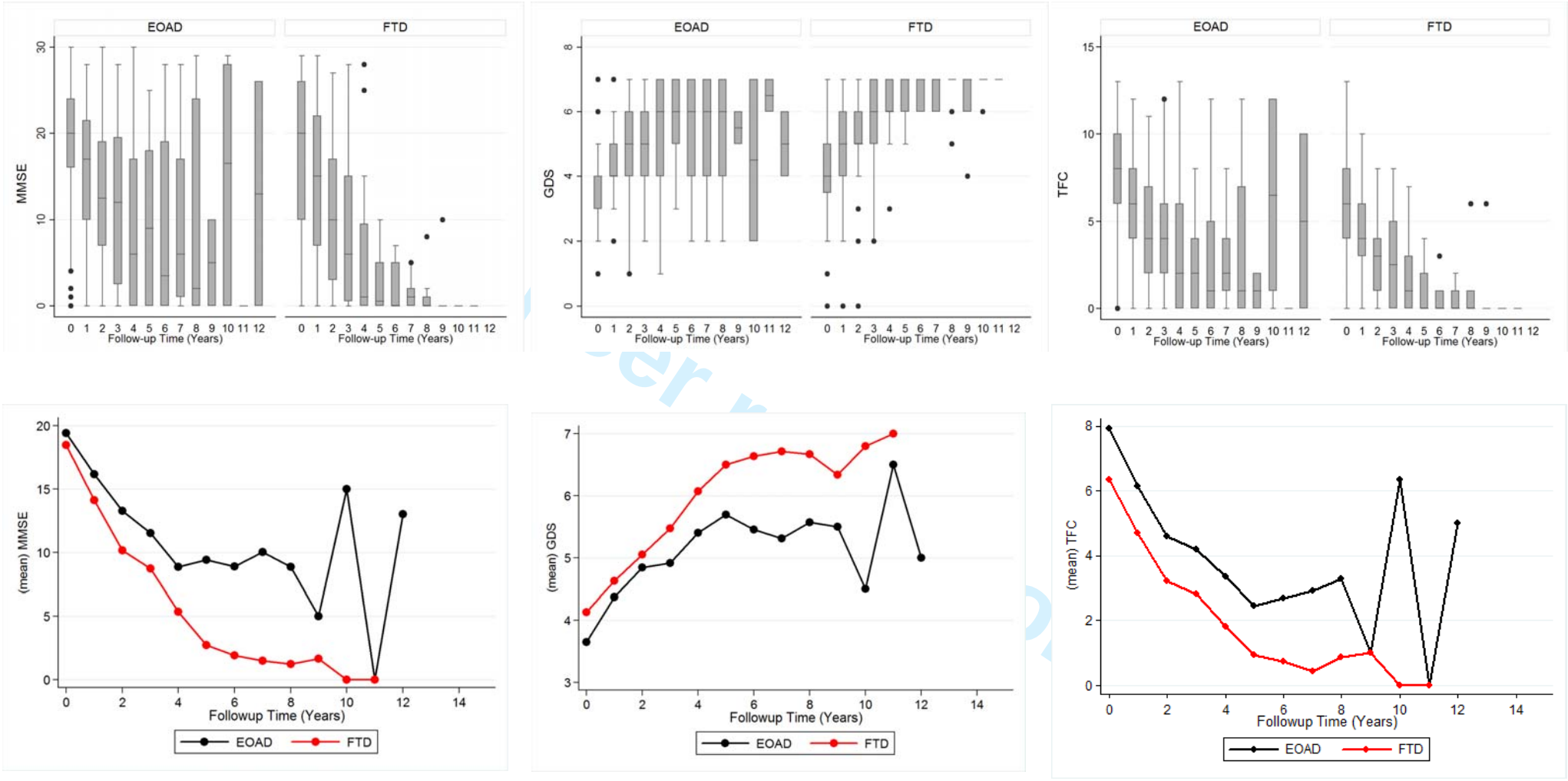

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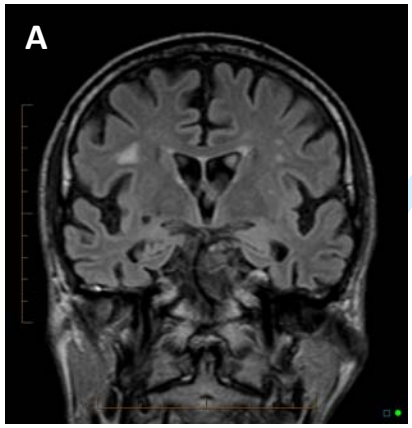

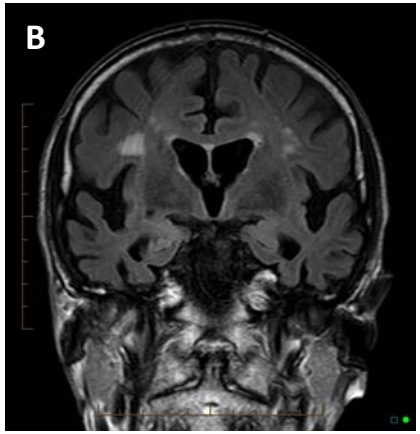

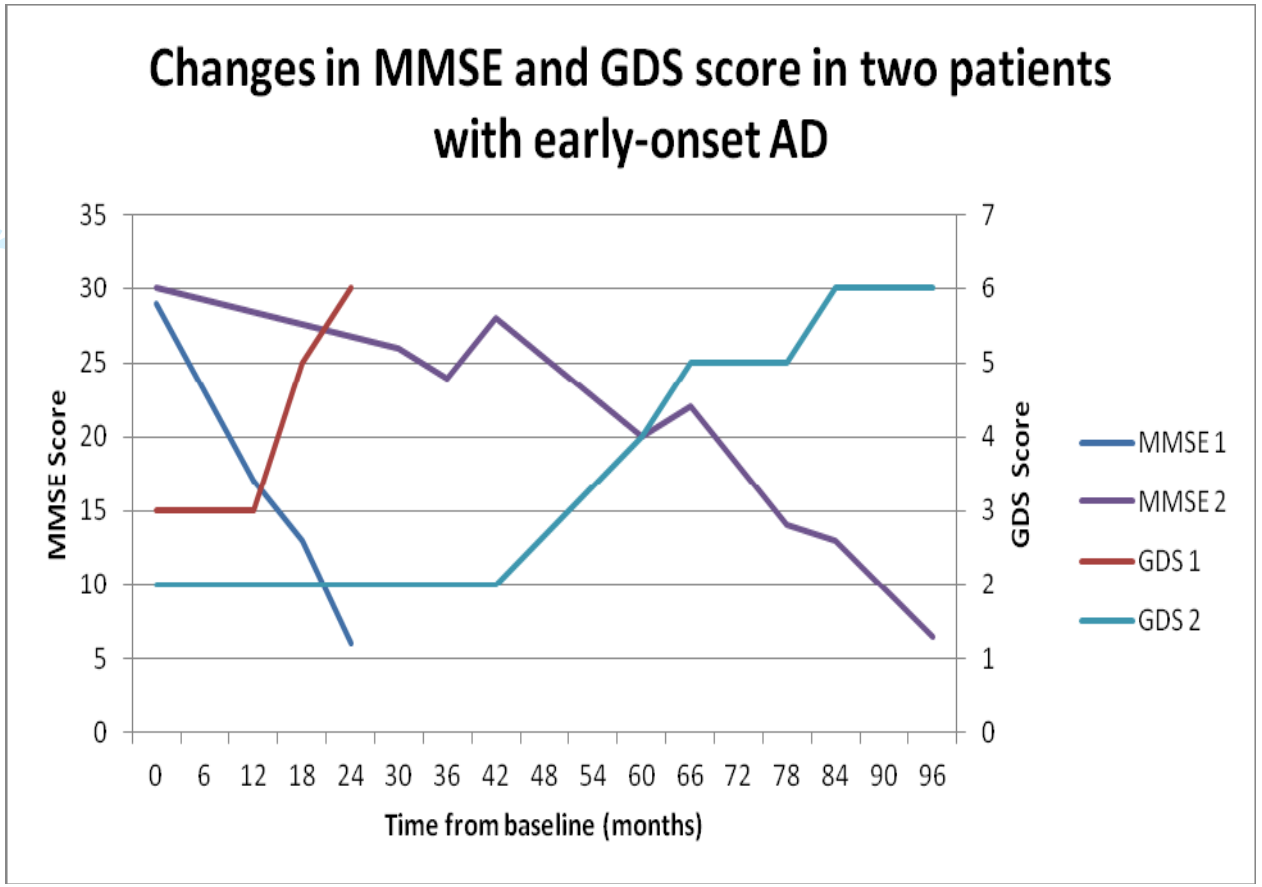

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The natural history of early-onset dementia: the Artemis Project ~~– a cohort study~~

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REVISED - AUGUST 2012

Key words: early-onset dementia, Alzheimer's disease,

natural history, fronto-temporal dementia

Abstract word count = 270 words

Text word count = ~~2189~~ 2358 words

References = 22

Tables = 3

Figures = 3

SUMMARY

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Key message: The difference in survival in patients with AD and FTD in our cohort might relate to the development of one or more cerebrovascular risk factors in FTD patients.

Strengths and limitations: A longitudinal prospective cohort of patients with a good sample size and long duration of follow-up using brief robust clinical measures.~~.~~ The limitations of this study are that the investigation was performed at a single study centre and more comprehensive assessments of memory and executive functions need to be performed in future studies.~~Future studies will allow more comprehensive assessments of memory and executive functions.~~

ABSTRACT

Objectives: The natural history of early-onset Alzheimer's disease (AD) and fronto-temporal dementia (FTD) remains to be described in detail. We seek to describe the natural history of early onset AD and FTD in terms of changes in cognitive assessment and staging, medical history and survival.

Design: ~~Case control~~Longitudinal prospective cohort analysis.

Setting: Neurodegenerative disorders research clinic.

Participants: 155 consecutive patients with clinically confirmed sporadic early-onset AD or FTD at a neurodegenerative disorders research clinic in Subiaco, Western Australia (The Artemis Project).

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Results: Patients with FTD were more likely to have a family history of dementia (p=0·026), to develop at least one cerebrovascular risk factor (p=0·003), manifest depression (Fisher's exact p=0·007), and to die during the follow-up period (Pearson chi-square 8·97, p=0·003). Kaplan-Meier survival estimates revealed a highly significant difference in the proportion of patients surviving the follow-up period (log rank 7·25, p=0·007) with FTD patients experiencing poorer survival than those with AD. The mean MMSE and TFC were consistently lower in those with FTD compared with those with AD over a decade of follow-up; mean GDS were consistently higher in those with FTD over the follow-up period.

Conclusion: We believe that the difference in survival in patients with AD and FTD in our cohort might relate to the development of one or more cerebrovascular risk factors in FTD patients and the severity of the underlying pathology.

OBJECTIVES

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METHODS

This study is a longitudinal prospective cohort analysis of a group of patients identified in a neurodegenerative disorders research clinic in Subiaco, Western Australia, from 1 January 1994 until 31 January 2011: The Artemis Project. The Artemis Project is an attempt to study the neurobiology of early onset dementia of all causes in Western Australia. Participants consisted of 155 patients with clinically confirmed sporadic early-onset Alzheimer's disease or fronto-temporal dementia, with onset prior to 65 years, who gave informed consent and attended the clinic on more than one occasion.

Patients with early onset AD were diagnosed using NINCDS-ADRA criteria and supported by structural and functional imaging (FDG PET) and neuropsychometry.[3,5,6] Patients were diagnosed with FTD using existing published criteria[7] and refined as new technology (such as FDG PET) became available[6] and at annual review using contemporary international guidelines.[3,8] With this approach, no patients have been excluded and our neuropathological sensitivity and specificity for the diagnosis of AD and FTD = 100%.

The FTD group comprised only of patients with the behavioural variant of FTD for uniformity of analysis; patients identified with semantic dementia (n=1), primary progressive aphasia (n=8) and motor neuron disease – FTD complex (n=2) were not included.

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Age at onset was determined from self and carer/spouse report of the onset of symptoms. Education is defined as self-reported years of formal education. Family history is defined as a self-reported family history of dementia in first- and second-degree relatives. Cerebrovascular risk factors are hypertension, hypercholesterolaemia, increased girth, obesity, diabetes, smoking, excessive alcohol consumption, coronary heart disease and peripheral vascular disease, the measurement of these has been described elsewhere.[9] The presence of at least one of these risk factors was determined from self-report and medical notes. The presence of mental illness (depression or psychosis) or other co-morbidities was also determined through self-report, carer information and medical notes.

Mini mental state exam (MMSE) was performed at each visit as a measure of cognition.[10] Global Deterioration Scale (GDS) and Total Functional Capacity (TFC) staging were determined for each visit as markers of the severity of the dementia and abilities to perform acts of daily living.[11,12] The ratings were performed by the same trained team of cognitive assessors.

DNA screening was performed on our patients with an autosomal dominant pattern of inheritance – nucleotide changes in the coding sequences of the amyloid precursor protein (APP), progranulin gene, presenilin–1 and presenilin–2 genes, Tau and SIGMAR 1 gene were performed by direct sequencing of

polymerosechoid reaction (PCR) products derived from genomic DNA. Nucleotide sequence information from each PCR product was obtained from both strands and possible mutations were verified by an independent amplification of the PCR product and resequenced. ApoE genotypes were determined by restriction fragment polymorphism analysis of PCR amplified products. Individuals identified with presenilin–1 mutation (Q222H), progranulin mutations and SIGMAR 1 mutations are not included in this study and will be reported elsewhere.

Statistical analyses, including chi-square tests for difference in proportions, t-tests for difference in means, and Kaplan-Meier survival analysis, were performed using Stata VII. As the MMSE and other variables are not normally distributed, the t-test was not used and the Kolmorgorov-Smirnov test employed to test for differences in means. No assumptions were violated for the Log-Rank test, nor drawing of the Kaplan-Meier curves – this is a non-parametric method. The Proportional Hazard Model was not used, which expects the baseline hazards for the two groups to be proportional.

RESULTS

The cohort consists of 155 early-onset dementia patients (92 with AD, 63 with FTD) (Table 1). Fifty-eight patients died during the study (AD = 25; FTD = 32); there were no drop-outs as spouses, carers and families remained in communication with study staff – even if admitted into nursing homes. There was a slightly greater, though not significant, proportion of males in the AD group compared with the FTD group (Pearson chi-square 2·76, p=0·096). The mean age of onset was similar between diagnosis groups for males (56·46 years vs. 55·73 years, p=0·583) and females (56·24 years vs. 55·60 years, p=0·670). Both groups had an average 11 years of education (p=0·900). Patients with FTD were more likely to have a family history of dementia (p=0·026), at least one cerebrovascular risk factor (p=0·003), a history of major depression diagnosed using DSM-IV criteria and distinguishable from apathy commonly found in FTD (Fisher's exact p=0·007), and to die during the follow-up period (Pearson chi-square 8·97, p=0·003). The cerebrovascular risk factors revealed a preponderance of

diabetes, smoking and increased alcohol consumption in the patients with FTD (Table 2). Kaplan-Meier survival estimates revealed a highly significant difference in the proportion of patients surviving the follow-up period, as can be seen in Figure 1 (log rank 7·25, p=0·007). There was no effect of APOE ε4 allele on the natural history of early onset Alzheimer's disease.

The mean MMSE was consistently lower in those with FTD compared with those with AD over a decade of follow-up (Figure 3). At baseline the MMSE, TFC and GDS did not show any significant difference between AD and FTD, providing further evidence for a worse progression of early onset FTD in comparison to AD. The boxplot shows that spread of MMSE scores is more condensed in those with FTD compared with AD across follow-up time. Similar results were seen with TFC. A greater range of GDS scores were seen in FTD patients compared with AD patients at baseline; however, a more condensed range of scores was seen across follow-up time. Mean GDS was consistently higher in those with FTD over the follow-up period. Some of the boxplots are missing (eg, year 11 for EOAD and years 9 and 10 for FTD): this is because median value is 0, min=0, max=0 so there is no box; for year 12 there is no data, hence no box. The unusual distribution beyond 9 years is likely due to small sample size, which would also be affecting the boxplots. It is possible there is a survival effect; those few who survive to that point and with longer follow-up may have a slower disease progression. The boxplots may also be affected by a clustering of scores at zero.

The majority of patients had a GDS score of four at baseline with a mean 4·02 years of follow-up (Table 3).

A graph of the changes in MMSE and GDS in two patients with early onset AD is presented in Figure 3 to highlight the heterogeneity in natural history in individual patients which may be overlooked in a cohort analysis. Patient 1 has no cerebrovascular risk factors and remained cognitively stable for a period of eight years. Patient 2 progressed rapidly over a period of two years. He was hypertensive,

smoked and consumed excessive alcohol. The magnetic resonance imaging shows white matter hyperintensities and progressive atrophy over this time. We did not observe such wide variation between FTD patients. White matter hyperintensities were identified in 10 patients with early onset AD (10.9%) and no patients with AD had evidence of small or large vessel ischaemia – apart from patient 2 (Figure 3) there was no correlation in other patients with white matter hyperintensities, prognosis and survival. No patients with FTD had white matter hyperintensities or evidence of stroke (small and large vessel).

DISCUSSION

A greater proportion of patients with FTD had a family history of dementia compared with AD patients. This is a similar result to those reported by Pasquier and colleagues.[13] They found a family history of dementia to be similar between AD and FTD patients, but a family history of dementia or psychiatric disorder to be much greater in FTD patients.[13] We are currently investigating further the role of family history as a risk factor in early-onset AD and FTD.

The difference in depression between those with FTD and those with AD is a complex issue. It may be that those with a history of depression are more at risk of FTD, or that patients with FTD are more likely to develop depression.

We found a difference in the MMSE, GDS and TFC between AD and FTD patients during the progress of the study, but not at the commencement of the study. The greater decline in MMSE in FTD patients might be attributable to the more aggressive nature of the dementia in FTD: findings supported by the changes in the functional scales and the differences in survival.

We sought to describe the natural history of early-onset dementia, particularly AD and FTD. We found that survival is significantly reduced in those with FTD compared with those with AD, as seen by

Koedam and colleagues.[4] In contrast, Pasquier and colleagues found survival to be similar between patients with AD and FTD after controlling for sex, age, age at onset and education level, although they did find sudden death to be more frequent in FTD.[13] This differences may be related to the inclusion of older onset dementia patients in this study. There was approximately a decade difference in mean age between Pasquier's AD and FTD patients while mean average was the same in our population. We speculate that the difference in survival between AD and FTD in our cohort might relate to the greater presence of one or more cerebrovascular risk factors in FTD patients – an unexpected finding. While our previous research had identified hypertension to be a risk factor in the development of AD, it does not appear to affect survival. Other elements of cardiovascular risk including smoking, increased alcohol consumption and obesity may develop in FTD as part of the frontal disinhibition syndrome and these factors may impact on survival. We need to be mindful of the risk profile in individuals with early onset AD as management of cerebrovascular risk factors will affect progress (Figure 3).

Our experience of different rates of progression in AD appears to be similar to the results of Thalhauser and Komarova.[14] They used a different staging system, the functional assessment staging (FAST) procedure and found that if a patient progressed rapidly through a FAST stage he or she was likely to experience rapid progression through the remaining stages (similar to the patient described in Figure 3). It has been found that comorbidity can be associated with an increased disease progression,[15] and this reflects our experiences with patients like Patient 2 (Figure 3). Additionally, poor physical health in those with AD is linked to poorer survival.[16] Work by Paradise and colleagues modelled survival time from age, constructional and gait apraxia in a much older cohort (mean age 81 years). These patients experienced shorter survival (approximately three years), likely due to the age of the population studied, whilst others found a median survival of 6.7 years in a younger group of AD patients aged 60-69 years.[17,18] While determining the predictors of survival in older age groups, Wolfson and colleagues were unable to determine the estimated probability of survival in early-onset AD after adjustment for rapid progression (length bias) because of a small early-onset sample size.[19]

Rapid versus slow progression may be related to structural and functional changes in the brain. Kim and colleagues suggested that a greater degree of glucose hypometabolism in the brain at the same level of dementia severity in early-onset versus late-onset AD patients might reflect rapid disease progression.[20] Sluimer identified that more generalised whole-brain atrophy may reflect rapid disease progression in comparison with more localised hippocampal atrophy in slow progressing AD;[21] Karas suggested the precuneus as a marker for progression of early-onset AD.[22]

The major limitations of this study are the measures used to follow patients and future studies will benefit from a more comprehensive memory assessment and more sophisticated measures of frontal lobe functions. Multicentre studies with larger numbers of patients will help to elucidate further the natural history of early onset dementia.

CONCLUSION

In conclusion we have described the natural history of early onset AD and FTD, and observed that patients with FTD progress faster than those with AD: a finding which might relate to the development of cerebrovascular risk factors during the course of the illness and differences in aggression of the underlying pathology. Larger multicentre studies with neuropathological confirmation are necessary to confirm these findings.

AUTHORS' CONTRIBUTIONS

ERA helped collect and collate data; analyzed data; and ~~helped draft~~wrote the manuscript.

MKB helped analyze data;~~a and~~ performed the statistical analyses; and helped draft the manuscript.

PKP collected data; collated and analyzed data; and ~~helped draft~~wrote the manuscript.

CONFLICTS OF INTEREST

~~The authors have no conflicts of interest.~~York Neuroscience Discover Inc (YND) is a charitable organisation operating under Australian law as a fundraising gift recipient that supports the research of Neurodegenerative Disorders Research Pty Ltd (NDR), a not-for-profit organisation devoted to the understanding of neurodegenerative disorders in young adults. YND is a tax deductible gift recipient governed by rules of association and a committee of management (ABN: 89 852 108 912). PKP is the Director of both NDR and YND; ERA is a Research Assistant of NDR.

FUNDING

This project was funded by York Neuroscience Discovery Inc, which was not involved in the conduct of the study, data interpretation or decision to publish.

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Table 1: Patient characteristics

Characteristic	AD (n=92)	FTD (n=63)
Sex, male, n (%)	43 (53·35)	38(46·91)
Age at onset, mean (std dev) - male - female	 56·46 (5·84) 56·24 (5.99)	 55·73 (6·04) 55·60 (6.42)
Education, years, mean (std dev)	11·08 (3·30)	11·01 (2·96)
Family history of dementia, n (%)	15 (16·48)	20 (31·75)[a]
Cerebrovascular risk factors present, n (%)	20 (21·98)	28 (44·44)[b]
Depression, n (%)	10 (10·99)	14 (22·22)[b]
Cancer, n (%)	2 (2·17)	3 (4·76)
MMSE, mean SD	21 (7)	21(7)
TFC, mean SD	8·7 (2·6)	7·2 (2·7)
GDS, mean SD	3·3 (1·1)	3·9 (1·1)
Deceased, n (%)	25 (27·17)	32 (50·79)[b]

a: p-value <0.05; b: p-value<0.01

Table 2: Cerebrovascular risk factors in early onset dementia

Risk factor	AD (n=92)	FTD (n=63)
Hypertension	16	7
High cholesterol	11	12
Increased girth	11	14
Obesity	8	10
Diabetes	3	8
Current smoker	5	14
Moderate or excessive alcohol consumption	5	13
Coronary heart disease	9	4
Peripheral vascular disease	2	1

Table 3: Mean follow-up in years by baseline GDS score

GDS stage at baseline	n	Years of follow-up, mean (std dev)
1	6	7·70 (3·88)
2	20	4·40 (1·98)
3	43	3·15 (2·27)
4	62	4·02 (3·09)
5	21	2·22 (2·48)
6	2	0·74 (0·42)
7	1	0·82 (-)

Figure 1: Survival analysis of early-onset AD and FTD patients in time (years) from baseline visit

Figure 2: Boxplot and line graphs showing the change in distribution and mean MMSE, GDS, and TFC score over time. Note the large variation in score from nine years onward is the result of a small sample size at those time-points.

Figure 3: Changes in MMSE and GDS score in two patients with early-onset AD. Patient 1 experienced a rapid deterioration, whilst patient 2 experienced slower disease progression (both patients were APOE ε4 homozygous). Patient 1 had no cerebrovascular risk factors. Patient 2 had poorly controlled hypertension, smoked and consumed excessive alcohol. His MRI revealed progressive atrophy and increase in white matter hyperintensities (A = baseline; B = 24 months).