PEER REVIEW HISTORY

This paper was submitted to the JNNP but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open where it is re-reviewed and accepted.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The natural history of early-onset dementia: the Artemis Project
AUTHORS	Panegyres, Peter; Atkins, Emily; Bulsara, Max

VERSION 1 - REVIEW

REVIEWER	Amboni, Marianna policlinico federico II, neurological sciences
REVIEW RETURNED	24-Apr-2012

GENERAL COMMENTS	In the present longitudinal cohort Study Atkins et al aimed to describe the natural history of early-onset Alzheimer disease (AD) and fronto-temporal dementia (FTD). The argument is relevant since dementia constitutes a major clinical and social problem due to the worldwide population aging, therefore trying to describe the features characterizing natural history of cognitive decline represents a challenging and priority issue. This Study has two main strengths: the relatively large sample size and the long follow-up duration. Nevertheless, a number of points should be reviewed . Points to be reviewed: 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?) 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. 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? 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 not difference, this finding should be discussed thus representing a possible further evidence for a worse progression of early-onset FTD vs early-onset AD. 5) Figure 2 shows a weird distribution: how do the Author 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). 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.

REVIEWER	The below review was originally submitted to the Journal of Neurology, Neurosurgery and Psychiatry. The reviewer gave permission for BMJ Open to publish their comments on the condition that their identity remained anonymous."
REVIEW RETURNED	24-Apr-2012

GENERAL COMMENTS	In this article the authors investigate the course of early-onset Alzheimer's disease and Fronto-temporal dementia, focusing on cognitive, staging, medical history and survival aspects. This is a very relevant area of study in order to improve the diagnosis and treatment of early-onset dementia. The cognitive and staging tools are well suited allowing a brief but relevant and sufficient characterization of cognitive and functional aspects. In future studies it would be interesting to see other cognitive tests included at least for memory and executive functioning domains, such as the CVLT and the D-KEFS Sorting Test, for example. The inclusion of single cases is also valuable because they contrast and encompass the heterogeneity in natural history of individuals with the group findings. In the Discussion section the authors provide a clear and thorough evaluation and interpretation of the results done in relation to previous research and the research problem. 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.

- The manuscript received a third review at Journal of Neurology, Neurosurgery and Psychiatry but the reviewer did not give permission for their comments to be published.

VERSION 1 – AUTHOR RESPONSE

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.

VERSION 2 – REVIEW

REVIEWER	Amboni, Marianna policlinico federico II, neurological sciences
REVIEW RETURNED	09-Aug-2012

GENERAL COMMENTS	In the present longitudinal cohort Study Atkins et al aimed at describing the natural history of early-onset Alzheimer disease and fronto-temporal dementia. The argument is relevant since dementia constitutes an increasing clinical and social problem due to the worldwide population aging, therefore trying to describe the features characterizing natural history of cognitive decline represents a challenging and priority issue. This study has two main strengths: the relatively large sample size and the long follow-up duration. The Authors have addressed all the points to review. I state that I have no competing interests in reviewing this manuscript. Marianna Amboni, MD PhD, IDC Hermitage-Capodimonte, Naples and CEMAND, University of Salerno, Italy.