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PARENTS' LONGEVITY AS A PROTECTIVE FACTOR FOR ALZHEIMER'S DISEASE

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PARENTS' LONGEVITY AS A PROTECTIVE FACTOR FOR ALZHEIMER'S DISEASE

LONGEVIDADE DOS PAIS COMO FATOR PROTETOR PARA DOENÇA DE ALZHEIMER

Trabalho final do 6º Ano do Mestrado Integrado em Medicina da Faculdade de Medicina da Universidade de Coimbra.

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Abstract

Introduction: Despite great effort to identify risk factors for developing Alzheimer's disease (AD), much remains to be understood. Some studies report association between longevity of an individual's parents and incidence of AD, with conflicting results. Furthermore, the role of sex-differential in parents' longevity and dementia remains particularly unexplored.

Aim: To investigate whether parents' older age at death may act as a protective factor for AD.

Methods: We performed a case-control study in Coimbra Hospital and University Centre. Cases were defined as adult patients with diagnosis of AD according to current criteria. Controls were defined as adults with normal cognitive performance, and no neuropsychiatric disorder. A structured questionnaire was applied to all subjects. Multivariate analysis was conducted with logistic regression to identify independent variables associated with status (control vs. cases). Statistical significance was set at $\alpha=0.05$.

Results: We included 225 subjects, 111 AD patients and 114 controls. We found mothers' age at death to be significantly higher in control vs. AD group (81.6 ± 12.3 vs. 77.2 ± 13.7 years, p=0.015). No difference was found between fathers' age at death (75.0 ± 13.8 vs. 74.0 ± 15.4 years, p=0.552). If we exclude patients and controls with a positive family history for dementia, the results are similar. On logistic regression, maternal age at death (OR=0.969, 95%CI= [0.947, 0.992], p=0.008) persists as statistically significant.

Discussion and Conclusion: Older maternal age at death appears to act as a protective factor for AD. This sex-differential in parents' longevity provides further insight on a possible maternally inherited risk factors in AD, deserving further investigation.

Keywords: Longevity, Dementia, Age, Alzheimer's disease, Heritability

Resumo

Introdução: Apesar de um grande esforço na identificação de fatores de risco para o desenvolvimento da doença de Alzheimer (DA), ainda há muito para descobrir. Alguns estudos já tentaram reportar uma associação entre a longevidade dos pais de um indivíduo e a incidência de DA, registando-se resultados contraditórios. Além disso, o papel da diferença de sexo na associação entre longevidade dos pais e demência permanece particularmente inexplorado.

Objetivo: Investigar se a morte dos pais em idade mais tardia pode funcionar como um fator de proteção para a DA.

Métodos: Realizámos um estudo de caso-controlo no Centro Hospitalar e Universitário de Coimbra. Os casos foram definidos como doentes adultos com diagnóstico de DA de acordo com os critérios atuais. Os controlos foram definidos como adultos com desempenho cognitivo normal, e sem alterações neuropsiquiátricas. Foi aplicado um questionário estruturado a toda a amostra. A análise multivariada foi realizada com regressão logística de forma a identificar variáveis independentes associadas ao estado (controlo vs. casos).

Resultados: Incluímos 225 indivíduos na amostra, 111 doentes com DA e 114 controlos. Verificámos que a idade de morte da mãe é significativamente maior no grupo controlo vs. DA (81.6 ± 12.3 vs. 77.2 ± 13.7 anos, p=0.015). Não foi encontrada diferença entre a idade de morte do pai (75.0 ± 13.8 vs. 74.0 ± 15.4, p=0.552). Se excluirmos os doentes e controlos com história familiar positiva para demência, as diferenças permanecem. Na regressão logística, a idade da morte da mãe (OR=0.969, 95%CI= [0.947, 0.992], p=0.008) persiste estatisticamente significativa.

Discussão e Conclusão: A morte da mãe em idade mais tardia parece funcionar como um fator protetor para a DA. Esta diferença de sexo na influência da longevidade dos pais fornece uma visão adicional sobre possíveis fatores de risco para DA, onde a mãe tem um papel preponderante, merecendo uma investigação mais aprofundada.

Palavras-chave: Longevidade, Demência, Idade, Doença de Alzheimer, Hereditariedade

Background

Alzheimer's disease (AD) is the most common form of dementia and the most prevalent neurodegenerative disease. [1] It is associated with cognitive decline, predominantly affecting episodic memory, but also involving other cognitive functions, such as language, problem-solving and visuo-constructive abilities. [2] Despite great effort to investigate this disease, much remains to be understood.

Research into risk factors for developing AD has uncovered multiple determinants [3], but there are probably much more to be discovered. Aging is known to dramatically increase the incidence and prevalence of AD. [3] Additionally, there is some evidence that AD is associated with the number of post reproductive years, rather than linear aging. [4]

AD is a highly heritable condition, with an estimated heritability of up to 80%. [5] One could therefore expect that if positive family history is a risk factor for AD, as it is virtually for most diseases, great longevity without disease in one's parents may act as a protective factor in descendants. In fact, it has been documented that centenarians may have a reduced incidence of AD, [6] suggesting that there are some underlying resilience factors, many probably genetic.

Longevity is considered reasonably heritable, [7] although it has been shown that assortative mating may be a factor responsible for this heritability. [8] Recently, *KLOTHO*, a gene shown to be associated with longevity, [9] has been demonstrated to protect against AD. [10] Moreover, the apolipoprotein E (*APOE*) gene, which is the main genetic risk factor for AD [3], has been shown to have a central role in longevity, [11] with the AD protective *APOE* ε2 allele being more prevalent in cognitively normal centenarians.[6]

The connection between longevity of an individual's parents and incidence of AD is still scarce. Effectively, Corkin S. *et al.* were the first to test this hypothesis, failing to find evidence. [12] Additional studies suggested a protective association connecting parents' longevity with less cognitive decline and dementia in descendants. [13-16] Recently, Tian Q. *et al.* neuroimaging work demonstrated that patients with at least one parent surviving to the age of 85 was associated with preservation of brain structures, such as temporal areas including the hippocampus. [17]

One interesting feature is the apparent prominence of mother's longevity influence in the reported findings [17]. Despite that, only one previous study directly looked for these differences. Bigarella R. *et al.* found a greater risk of dementia in subjects with a mother's age at death younger than 60, not finding any link with the father's age at death. [18]

To the current day, there has been a holistic approach of parents' longevity and cognitive decline, not focusing on individual neurocognitive disorders. Furthermore, the role of sex-differential in parents' longevity and dementia remains particularly unexplored. In this study, we aim to investigate whether later age of parents' death may act as a protective factor for AD. Additionally, we aim to study a possible role of sex-differential in parents' longevity and the risk of AD.

To explore this possibility, a thoroughly characterized AD cohort of Coimbra Hospital and University Centre (CHUC) Memory Clinic was assessed and a case control study was conducted.

Methods

Study design

This case control study was conducted in the Coimbra Hospital and University Centre (CHUC) Memory Clinic, department of Neurology between October and December 2020. Ethical approval for the study was obtained from the CHUC Ethical Commission (CES 226) and consent was obtained from all participants. The principles of the declaration of Helsinki were fully fulfilled.

Cases and controls

Cases were selected by convenience sampling from Dementia consult of CHUC Memory Clinic. Patients older than 18 years old and diagnosed with Alzheimer's disease (AD) by the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease [2] were eligible. All the patients included had cerebrospinal fluid biomarkers supportive of AD diagnosis.

Controls were recruited from a variety of settings including the CHUC Outpatient Memory Clinic and the emergency department of CHUC, after written consent. Controls older than 75 years, with normal cognitive performance, and with no neurological or psychiatric disorder were eligible.

Exclusion criteria

Subjects with severe chronic health conditions (except for Alzheimer's disease in the group of cases) were excluded. Patients and controls from whom a valid consent could not be obtained were excluded.

Data Collection

Structured interviews were performed by the investigators participating in this study. It was applied a questionnaire designed for this study (Annex I), regarding demographic and past medical family history. The questionnaire specifically asked about date of birth, age of onset (AOO) of AD (for patients), years of education and place of birth of the subjects. Concerning the family history, we asked about history of known consanguinity, age at parents' death, cause of parents' death, place of birth, history of past neuropsychiatric disorders or any other relevant disease. Particularly, regarding self-reported family history of dementia or cognitive dysfunction, a sequence of questions was asked (Did he/she have problems with his/her memory?, Was he/she able to recognize all the relatives?, Was he/she able to perform all the

daily chores?, Was he/she able to go outside alone and not get lost?). The same information was collected about the siblings and offspring of the subjects. Additionally, the phratry was registered in order to facilitate future reconstruction of family pedigrees.

Statistical analysis

Data were analysed using IBM Statistical Package for the Social Sciences (SPSS), 25th version. Normality of the distributions was assessed with Shapiro-Wilk test. Categorical variables are represented using frequencies and were compared through chi-square tests. Mann-Whitney test and independent samples T-student were used to determine significant differences in the quantitative variables between cases and controls. Correlations between quantitative variables were measured using Pearson correlation. Multivariate analysis was conducted with logistic regression, to identify independent variables associated with status (control vs. cases). The significance level was defined for alpha (α) of 0,05.

Results

We included 225 subjects, 111 AD patients and 114 controls (table 1). Patients were on average 71.83 (±8.6) years old and had 6.3 (±4.8) years of education. From the 111 AD patients, 71 were female (64.0%). Controls were on average 79.9 (±6.1) years old and had 5.3 (±4.1) years of education. From the 114 controls, 63 (55.3%) were female. Average AOO of AD patients was 65.4 (±8.1) years. Groups (controls vs AD patients) were statistically different in terms of age at evaluation, positive family history (both paternal and maternal) and mother's age at death (table 1).

Mothers' age at death was significantly higher in controls versus AD patients' group (p=0.015). AD patients' mothers died with an average of 77.2 (±15.4) years of age, while controls' mothers died with a mean age of 81.6 (±12.3) years (figure 1). Yet, no statistically significant difference was found considering the fathers' age at death (p=0.552). AD patients' fathers died with an average of 74.0 (±15.4) years of age, while controls' fathers died with a mean age of 75.0 (±13.8) years (figure 2). Regarding parents' age at death combined, although tending to significance, we did not find a statistically significant difference between controls versus AD patients' group (p=0.058).

Positive family history of dementia/cognitive dysfunction was also found to be significantly different. Considering maternal diagnosis, 25 of 110 AD patients (22.7%), versus only 11 of 113 controls (9.7%) had a mother with dementia/cognitive dysfunction (p=0,010). Paternal history was also significantly different, 18 of 109 AD patients (16.5%) versus only 6 of 113 controls (5.3%) had a father with dementia/cognitive dysfunction (p=0.009).

Considering these results, a further analysis was performed excluding patients and controls with a positive family history for dementia/cognitive dysfunction. AD patients' fathers died with a mean of 72.4 (±15.9) years of age versus 75.1 (±13.6) years of age of controls' fathers (p=0,426) while AD patients' mothers died with a mean of 75.2 (14.7) versus 80.5 (±12.6) years of age of controls' mothers (p=0.008).

On logistic regression (table 2), positive family history (odds ratio=3.010, 95% confidence interval=[1.605,5.643], p=0.001) and maternal age at death (odds ratio=0.969, 95% confidence interval=[0.947, 0.992], p=0.008) remain statistical significant.

	AD patients	Controls	p	Total
Age at evaluation (years)	71.8 (±8.6)	80.0 (±6.1)	**<0.001**	75.7 (±8.7)
Sex (%)	64.0	55.3	0.222	59.6
Education (years)	6.3 (±4.8)	5.3 (±4.1)	0.061	5.8 (±4.5)
Age of onset (years)	65.4 (±8.1)	-	-	-
Fathers' age at death/follow-up (years)	74.0 (±15.4)	75.0 (±13.8)	0.552	74.4 (±14.5)
Father with dementia/ cognitive dysfunction (%)	16.5	5.3	**0.009**	10.8
Mothers' age at death/follow-up (years)	77.2 (±13.7)	81.6 (±12.3)	**0.015**	79.5 (±13.0)
Mother with dementia/ cognitive dysfunction (%)	22.7	9.7	**0.010**	16.1
Parents' age at death/follow-up (years)	75.6 (±11.4)	78.3 (±9.4)	0.058	77.0 (±10.5)

Table 1: Demographic variables of patients, controls and their parents.
AD, Alzheimer's disease

	OR	95%CI	p
Positive Family History	3.010	1.605, 5.643	**0.001**
Female sex	0.606	0.333, 1.104	0.102
Education (years)	1.052	0.985, 1.124	0.133
Fathers' age at death/follow-up (years)	0.999	0.978, 1.019	0.888
Mothers' age at death/follow-up (years)	0.969	0.947, 0.992	**0.008**

Table 2: Logistic regression values (χ^2=24.927, p<0.00<, -2 log likelihood=296.496, R^2=0.148).
OR, Odds Ratio; 95% CI, 95% Confidence Interval

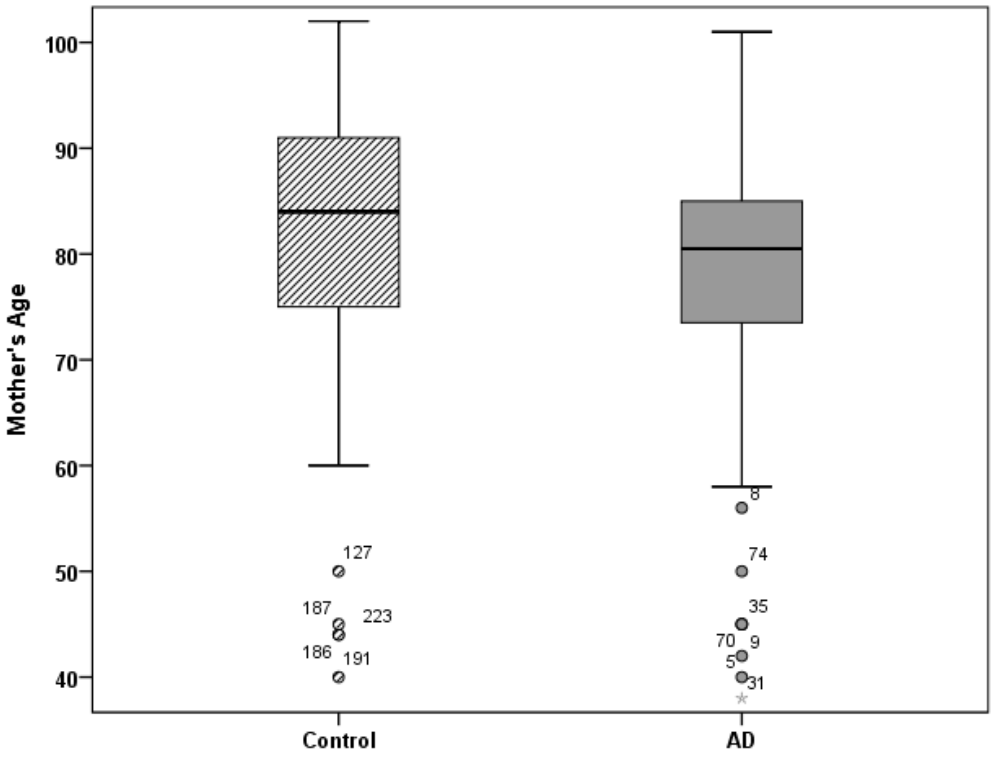

Figure 1: Mothers' age at death of patients and controls.
AD, Alzheimer's disease

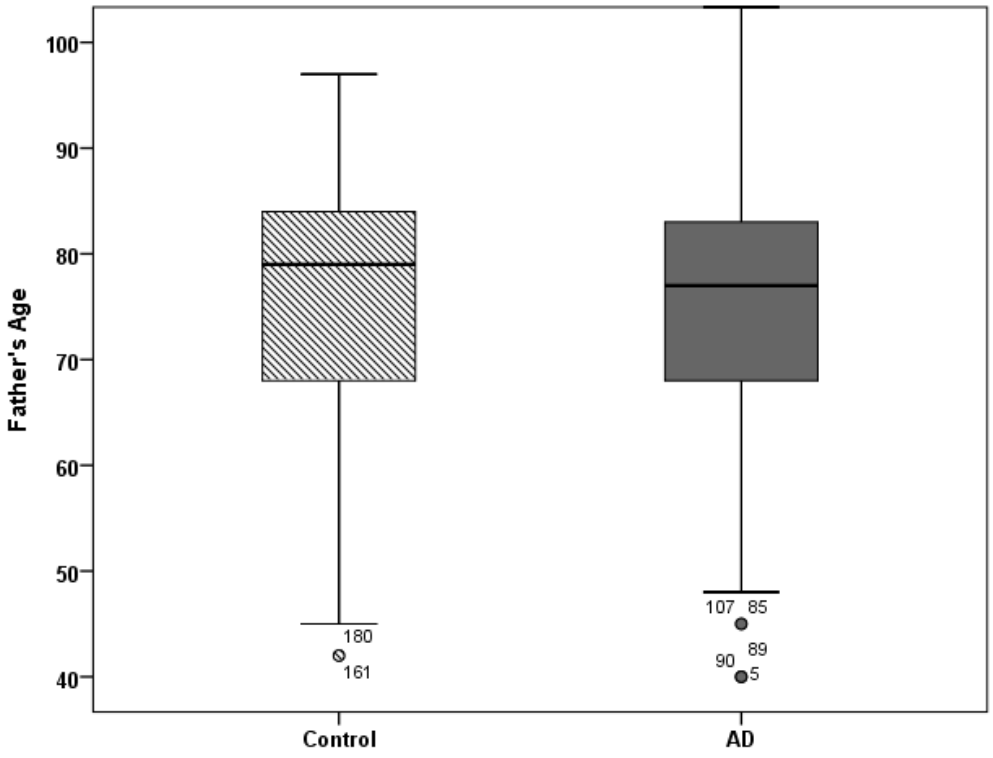

Figure 2: Fathers' age at death of patients and controls.
AD, Alzheimer's disease

Discussion

This study suggests that later maternal age at death protects against AD, while we could not find an association with paternal age at death. To our knowledge this is the first study designed specifically for AD, with the diagnosis supported by biomarkers.

Besides, we studied longevity through a continuous quantitative variable (years of age), instead of ranking groups based on arbitrary cut-off points to define parents with exceptional longevity versus usual survival, as done firstly by Lipton R. *et al.* [13]. Effectively, they established a cut-off point of 85 years of age and beyond, for defining the parents' group with exceptional longevity and proved that this group was associated with less development of dementia by their offspring, regardless of the progenitor sex. [13] Not clustering subject mothers and fathers in a single group allowed us to identify this parental sex difference in the risk of AD. These findings are supported by Bigarella R. *et al.* study, that failed to link the father's age at death with dementia in the offspring [18], but potentially conflicts with previous studies in which this sex-differential role was not reported [13-16]. Further research on this difference is needed.

The age at evaluation was significantly different (71.8 years for AD patients' vs 80 years for controls, $p<0.001$). This happened because we included many early-onset AD patients, while controls were included only if older than 75, to decrease the possibility of a future diagnosis of dementia. We believe this difference does not compromise the pattern of our results. On the contrary, by the increase in life expectancy on the last century, parents of older individuals would tend to die earlier, which could in fact reduce the power of our analysis and thus making our results even stronger. It also ensures that our controls are less prone to be cognitively impaired, due to the fact they are still mentally healthy in such an advanced age. Another slight mismatch was the higher education of patients vs. controls (6.3 years vs 5.3 years, $p=0.061$). We attribute this to the lower age of patients. Yet, this would again tend to minimize the power of our analysis, as education is a well-known protective factor for the development of AD [3]. The prevalence of female sex in the patients' group was also slightly superior (64.0% vs 55.3%, $p=0.222$). This could have some influence in the risk of developing AD as female sex is a known risk factor for this disease [3]. However, these differences are not significant, and we believe they did not affect our study internal validity.

Although we do not have pathological confirmation of either patients or controls, most patients have biological support of the diagnosis (cerebrospinal fluid biomarkers or amyloid-PET imaging). Controls were collected by an experienced cognitive neurologist and with at least 75 years of age in order to minimize the possibility of future development of AD.

Our data, showing that maternal age at death is related with the incidence of AD, suggests that maternal longevity may be a proxy of underlying factors that protect the brain from developing dementia. These may be genetic or environmental, but the fact that maternal longevity and not paternal longevity shows an association suggests that the most important factors would be genetic. This points to mitochondrial or X chromosome genetic or epigenetic factors, still to be identified and that could explain a part of the missing heritability in AD. [19]

Longevity studies, such as the well-known Framingham Longevity Study [20], reported that an individual's lifespan correlates with parents' longevity. In addition, it showed that the mother's age at death may have a superior impact in the offspring life expectancy than the father's age at death. [20]

We could not find an association between father's age at death and AD. However, we cannot exclude that paternal influence may be lower than the maternal influence and we may have not identified a connection with paternal longevity due to a reduced power. Besides, men tend to die earlier [21], which may complicate the understanding of this factor's effect, as ages at death tend to cluster more in men than in women.

This study has some limitations. Data was collected using a structured questionnaire, however unintentional recall bias could only be limited to a certain extent as some information was self-reported and patients' history was sometimes given by the spouse. Other possible confounding variables as low severity medical comorbidities (such as hypertension, diabetes mellitus) and other demographic and lifestyle factors were not assessed.

Further studies with a larger sample and stratification of participants according to *APOE* genotyping (major genetic risk factor for late-onset AD [3]), will provide further insight into the role of parents' longevity. Other possible interesting variables to analyse would be biomarker fluid levels and magnetic resonance imaging variables and their relationship with longevity in AD patients. Our work designed a digital database for CHUC Memory Clinic not only for this study but also for gathering a wider amount of data, such as family history and the possibility to draw family pedigrees. We intend to expand our sample size in order to clarify the paternal longevity role in AD risk and differences between patients' sex.

Conclusion

To our knowledge this is the first study designed specifically to investigate whether parents' later age at death may act as a protective factor for AD, with the diagnosis supported by biomarkers.

We concluded that later maternal age at death appears to act as protective factor for this disease. This sex-differential provides further support on maternally inherited risk factors in AD, which will ultimately contribute to new strategies of prevention and treatment.

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Annex I – Family Questionnaire for AD study.

Francisco Mano

Questionário Familiar_ Estudo Doença de Alzheimer

I. Dados do doente/controlo

i. Código de doente/controlo:
ii. Data de nascimento: ____/_____/_____
iii. Data de observação: ____/_____/_____
iv. Idade de início da doença (se aplicável): _____ anos
v. Escolaridade: _____
vi. Naturalidade: _____

II. História familiar

i. História de consanguinidade:

☐ Não existe ☐ Existe (descrever:_____

_____)

III. Dados do pai do doente/controlo

i. ☐ Falecido, idade de óbito: _____ anos ☐ Vivo, idade atual: _____ anos
   - Causa da morte (se aplicável): _____
ii. Naturalidade: _____
iii. Alterações cognitivas/demência:

☐ Não ☐ Sim (qual/quais: _____)

   - Idade de início: _____ anos

iv. Outras doenças neurológicas:

☐ Não ☐ Sim (qual: _____)

   - Idade de início: _____ anos

v. Doenças psiquiátricas:

☐ Não ☐ Sim (qual/quais: _____)

   - Idade de início: _____ anos

vi. Outras doenças de relevo:

☐ Não ☐ Sim (qual/quais: _____)

vii. Número de irmãos: _____ Posição na fratria: _____

IV. Dados do mãe do doente/controlo

i. ☐ Falecida, idade de óbito: _____ anos ☐ Viva, idade atual: _____ anos

- Causa da morte (se aplicável): _____

ii. Naturalidade: _____

iii. Alterações cognitivas/demência:

☐ Não ☐ Sim (qual/quais: _____)

- Idade de início: _____ anos

iv. Outras doenças neurológicas:

☐ Não ☐ Sim (qual: _____)

- Idade de início: _____ anos

v. Doenças psiquiátricas:

☐ Não ☐ Sim (qual/quais: _____)

- Idade de início: _____ anos

vi. Outras doenças de relevo:

☐ Não ☐ Sim (qual/quais: _____)

vii. Número de irmãos: _____ Posição na fratria: _____

V. Irmãos do doente/controlo

i. Número de irmãos: _____ Posição do doente na fratria: _____

Posição na fratria (deixar em branco a coluna da posição do doente)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Meio irmão (assinalar com X se aplicável)								
Sexo								
Se VIVO, idade atual								
Se FALECIDO, idade de óbito								
Causa de morte								
Alterações cognitivas/demência (sim ou não)								
Idade de início (se aplicável)								
Outras doenças neurológicas (sim ou não)								
Doenças psiquiátricas (sim ou não)								
Doenças de relevo (se sim, quais; se não, deixar em branco)								

VI. Filhos biológicos do doente/controlo

Posição na fratria	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Sexo								
Se VIVO, idade atual								
Se FALECIDO, idade de óbito								
Causa de morte								
Doenças de relevo (se sim, quais; se não, deixar em branco)								