Environmental and Genetic Risk Factors for Alzheimer's Disease in Spain

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Abstract

Alzheimer's disease is a complex neurodegenerative disorder of unknown aetiology, and an important number of cases are sporadic. To date, only some of the genetic and environmental risk factors for Alzheimer's disease have been identified. It is very important to understand the role of environmental and genetic risk factors in Alzheimer's disease in order to develop therapeutic strategies. For sporadic cases of Alzheimer's disease, many environmental and genetic risk factor modifiers have been described, but – with a few exceptions – most of them remain controversial. In this article we review some studies of these risk factors in a Spanish population to identify a few directives for future studies.

Keywords

Alzheimer's disease, environmental risk factor, genetic risk factor, age, education, cardiovascular risk factors, Spanish population

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Alzheimer's disease (AD) is a neurodegenerative disorder of unknown aetiology, with the exception of a small percentage of cases related to mutations of the amyloid precursor protein (APP), presenilins and other, as yet unknown, genes.[1,2] For sporadic cases of AD, many environmental and genetic risk factor modifiers have been described, but – with a few exceptions – most of them remain controversial. Most of these studies are observational in different populations,[3] since case–control studies, which were very popular in the 1980s, showed bias.[4] Unconfirmed associations of environmental risk factors or genetic traits with AD could be due to several factors, such as inclusion of a percentage of patients with erroneous diagnoses (a significant number of patients with clinical diagnoses of AD are found to have mixed pathologies or other diseases at *post mortem* examination), inadequate size or special characteristics of the sample or excessively permissive statistical evaluation.

Spain has several characteristics that make it adequate for such studies. Although in the past Spain has seen significant waves of immigration, in the last millennium immigration has not occurred at high enough levels to influence the genetic background of its population. Spain also has high-quality standards of universally free healthcare. Several studies have been published as meta-analyses[5] or local population studies.[6–9] In this article we review some of these and other, more recent, studies.

Environmental Risk Modifiers

A summary of the available data is shown in *Table 1*, which presents results about environmental modifiers of the risk of AD in other countries as well as in Spain.[3,5–14] We shall review briefly the most important results obtained in the studies performed in Spain. The most important studies reviewed in this work are those in Zaragoza and Pamplona,[5] Gerona,[6] the Basque Country,[9] Central Spain[7] and Leganes.[8] A brief summary of these studies is presented in *Table 2*.

Age

As in other studies around the world, epidemiological investigations performed in Spain have confirmed the increased risk associated with age in AD. This effect is almost exponential until >90 years of age, when it appears to reduce its impact.[10,15]

Education

Illiteracy and poor schooling are associated with an increased risk of dementia and AD in most studies in which the population has a mixed (assorted) educational background.[3,10,13,14] The same findings are reported in Spain.[5–9] However, most of these studies did not differentiate between education and its co-variates, such as low socioeconomic status, possible pre-natal and developmental nutrition, lack of social and familial intellectual stimulation and others.[16–19]

Gender

The majority of population-based studies performed in Spain have shown an increased risk of AD in females.[6,8,9] In the Neurological Disorders in Central Spain (NEDICES) study this relationship was not found.[7] This has been proposed as the basis for a neuro-protective role of oestrogens, even prompting the use of these compounds in clinical trials, but a very confusing factor is the fact that senile females (around the turn of the millennium this was defined as >65 years of age) had a much lower level of education than contemporary males. Studies such as the Ashkelon study where gender was corrected for by education have not shown a difference in the risk at different ages. As a meta-analysis pointed out,[10] there

Table 2: Epidemiological Studies on Environmental Risk Factors for Dementia in Spain*

Place	Munguía, Basque Country	Girona, Catalunya	Central Spain (2 in Madrid, 1 in Avila)	Leganes
Type of study	Population, >65 years of age, all persons	Population, >75 years of age	Population, >65 years of age, sample	Population, >70 years of age, sample
Temporal profile	Cross-sectional	Longitudinal follow-up	Longitudinal follow-up	Longitudinal follow-up
Type of population	Rural	Rural	Three subpopulations: • rural • urban, blue collar • urban, upper level	High proportion of immigrants from countryside to urban areas
Controls	1,756	1,260	4,972 →3,730	315
Dementia	175	300 at start + 125 new cases	306 →161	
AD	133		115	55
VD	15		18	
Other dementias	27		28	
AACD				157
Risk factors for AD (OR):				
Age	1.14–1.15	1.04–1.15	1.14–1.17	0.82–57.42
Gender (female)	1.67–1.97	1.0–3.4	NS	1.12–8.20
Stroke	3.00–7.84		1.35–4.82	0.56–7.64
Depression	3.19–53.08	NA	NS	NS
Statistics	Logistic regression	Logistic regression	Cox proportional hazard models	Logistic regression + Bonferroni correction

*AD = Alzheimer's disease; VD = vascular dementia; AACD = age-associated cognitive decline; OR = odds ratio. *Only the Spanish studies fully described are included in the table.*

Table 1: Environmental Risk Modifiers for Dementia and Alzheimer's Disease

	Dementia	AD
Age	↑↑	↑↑
Gender	↑	↑
Education	↑↑	↑↑
Cardiovascular risk factors:	↑↑	↑↑
Stroke	↑↑	↑↑
Heart disease	↑	↑
Diabetes	↑	↑
Smoking	↑↑	↑
High blood pressure	↑↑	↑
Obesity	↑	↑
Hypercholesterolaemia	↑	↑
Depression	↑	↑
Diet (Mediterranean)	↓	↓
Drug treatment:		
NSAIDs	↓	↓
Statins	↓	↓
Hormones	↓	↓
Severe head trauma	↑	↑
High social and intellectual activity	⇊	⇊

AD = Alzheimer's disease; NSAIDs = non-steroidal anti-inflammatory drugs; ↑ = incomplete evidence for increased risk factor; ↑↑ = strong evidence for increased risk factor; ↓= incomplete evidence for protective factor; ⇊= strong evidence for protective factor.

was no gender difference in dementia incidence, but women tended to have a higher incidence of AD in very old age and men tended to have a higher incidence of vascular dementia (VD) at younger ages. Another finding is that the pathological expression of AD could have more clinical relevance in women.[20]

Cardiovascular Risk Factors

The presence of cardiovascular risk factors has been considered, by definition, as an important criterion for the differentiation between AD and VD.[11] However, neuropathological studies have shown that such differentiation is unwarranted.[12] Even using the conventional international criteria for the diagnosis of AD and VD, all of the epidemiological studies have shown that high blood pressure, diabetes and previous history of stroke are risk factors for dementia in general, and VD and AD in particular.[21–24] It also appears that the risk of these factors is additive.[7,24,25] Some meta-analyses have shown that the treatment of high blood pressure reduces the risk of dementia.[26]

Lifestyle

Several studies have shown that physical exercise reduces the risk of dementia and AD.[3,27] Again, this co-variates with other social factors. The role of exercise has been downplayed on the basis of considering an excessively sedentary lifestyle as a prodromic symptom of dementia.[27] The beneficial effects of exercise in transgenic mice[28] and in patients[29] do not support this scepticism. Intellectual and social activities are considered protective against dementia and AD.[13] There is only one preliminary Spanish study on this topic in Spain.[30]

Epidemiological Studies of Environmental Risk Factors for Dementia and Alzheimer's Disease in Spain

A summary of the most important epidemiological studies performed in Spain is presented in *Table 2*. These studies are difficult to compare because of their different methodologies, but the results obtained are essentially similar.

Epidemiological Studies of Genetic Risk Factors for Dementia and Azheimer's Disease in Spain

Dozens of studies on genetic risk factors for dementia and AD have been performed in Spain, and a summary of the most important is presented in *Table 3*. The study performed by Ampuero et al.[8] was a population study and the results were validated in a pathological series. The other studies are case–control studies in clinical cohorts of patients without pathological confirmation of the diagnoses.

Table 3: Genetic Risk Factors for Alzheimer's Disease and Dementia in Spain

Gene	Protein Function	Variation	Type of Study	Effect	Reference
ApoE	Mediates the binding, internalisation and catabolism of lipoprotein particles	Allele ε4		Increased risk of AD	45
14-3-3 Zeta (tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta isoform) *Tau* (microtubule-associated protein tau)	The 14-3-3 family of proteins mediates signal transduction by binding to phosphoserine-containing proteins Promotes microtubule assembly and stability and might be involved in the establishment and maintenance of neuronal polarity	14-3-3 Zeta rs983583 + Tau rs2471738	CC	Decreased risk of AD 2.5-fold	31
IL-10 *CYP19* (aromatase)	Inhibits the synthesis of a number of cytokines, including IFN-gamma, IL-2, IL-3, TNF and GM-CSF produced by activated macrophages and by helper T cells Catalyses the formation of aromatic C18 estrogens from C19 androgens	IL-10 rs1800896 + CYP19 rs1062033	CC	Decreased risk of AD 6-fold	32
14-3-3 Zeta *BCHE* (butyrilcholinesterase) *14-3-3 Zeta* *BCHE*	Mutant alleles at the BCHE locus are responsible for suxamethonium sensitivity 14-3-3 zeta protein rs 983583+ BCHE Ala539Thr	14-3-3 zeta protein rs964917 + BCHEK variant	CC	Decreased risk of AD	33
CD14 *LXR Beta*		CD14 rs2569190 + LXRb rs1052533	CC	Decreased risk of AD 6-fold	34
BACE 1 *ApoE* *OLR1* *VLDLR*		BACE1 exon 5 G/C + ApoE ε4 3'UTR (+1071 A) + (+1073C) 5'UTR (CGG)n allele5		Increased risk of AD Increased level of astrocyte activation in AD Risk factor in Asian people but protective factor in Caucasians	35
ABCA1		Haplotype (R219K, I883M, R1587K)	CC	Increased risk of AD 1.75-fold	36
PRNP129 *IL-1A*		PRNP129 (Met129Met) + IL1A (-889 allele 2)	CC	Increased risk of AD 3.0-fold	37
ER α (ostrogen receptor alpha) *BCHE*		ER α (-401CC) + BCHEK variant	CC	Decreased risk of AD	38
PARP-1 (poly(ADP ribose) polymerase 1) *PARP-1* (poly(ADP ribose) polymerase 1) *IL-1*		PARP-1 haplotype (-410, -1672) PARP-1 haplotype (-410, -1672)+ IL1A (-889 allele2)	CC	Increased risk of AD	39
Glycogen synthase kinase-3 α STH (saitohin)		Glycogen synthase kinase-3 α (-50 TT promoter) + STH(Q7R)	CC	Increased risk of late-onset AD	40
BBH (dopamine beta-hydrolase) *IL-1* *IL-6*		BBH (-1021C/T promoter)+ IL-1(-889 allele 2) + IL-6 (-174 allele G)	CC	Increased risk of late-onset AD	41
CETP (cholesteryl ester transfer protein) *ApoE*		CETP -629 C/A+ ApoE ε4	CC	Decreased risk of AD approximately 3-fold in ApoE ε4 carriers	42
IL-6 *IL-6* *ICAM1* (intercellular adhesion molecule1)		IL-6 (-174 C/C) IL-6 (-174 C/C) + ICAM1 (K469K)	CC	Decreased risk of AD Decreased risk of AD	43
IL-6 *IL-10*		IL-6 (-174 C/C) + IL-10 (-1082 A/A)	CC	Decreased risk of AD 6-fold	44

AD = Alzheimer's disease; IFN = interferon; TNF = tumour necrosis factor; GM-CSF = granulocyte macrophage colony-stimulating factor; CC = case control study; R = review; IL = interleukin.

Table 4: Requirements of the Studies on Environmental and Genetic Risk Factors for Dementia and Alzheimer's Disease

Population-based studies are preferable to case–control studies.
Confirmation of the results by clinical–pathological series is warranted.
The sample size should be large, ideally >500 cases per group.
The sample should not be limited to a particular ethnic group.
The results should be replicated by other studies.
The statistical analysis should include logistic regression of multiple variables. The number of cases required increases with the number of variables investigated.
The risk factors identified should have functional relevance.

These studies of different genetic risk factors performed in case–control clinical cohorts are very promising since they provide an enormous amount of data. However, interpretation of the data is difficult due to the lack of definitive diagnoses and to statistical limitations. Therefore, the results require confirmation by other studies, clinical–pathological series and functional investigations.

In summary, the impact of the ApoEε4 allele appears as a significant risk factor for AD, while the other risk modifiers, although they have statistically significant value, did not demonstrate beyond any doubt their clinical relevance. The requirements of the optimal studies of risk factors are summarised in *Table 4*. ■

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