ALZHEIMER'S DISEASE AND AGE-RELATED MACULAR DEGENERATION

ENFERMEDAD DE ALZHEIMER Y DEGENERACIÓN MACULAR ASOCIADA A LA EDAD

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ABSTRACT

Objectives: We analysed different risk factors involved in the onset of both Alzheimer’s disease (AD) and age-related macular degeneration (ARMD). The putative relation between both disorders was studied.

Methods: We studied 57 subjects to determine the correlation between AD and ARMD. Thirty-three of the subjects suffered dementia (cases), whereas 24 of them (controls) did not. Firstly, anamnesis was performed for all individuals. We then examined the macular area of the eye using a non-mydriatic TRV-50VT fundus camera. Significant odds ratio (OR) results were used as a statistical tool to survey the putative link between AD and ARMD.

Results: The OR test results showed that ARMD was associated with Alzheimer’s disease. The occurrence of ARMD was significantly higher for cases (42.4%) than for controls (25%). On this basis, we inferred a cause-effect relation linking both variables. Our dataset suggested that the control group was more protected against ARMD than the case group, as revealed by Fisher’s exact test (P = 0.649).

ABSTRACT

Objetivos: Analizar diferentes factores de riesgo implicados en la aparición de la enfermedad de Alzheimer y de la degeneración macular asociada a la edad, tratando de establecer una relación de asociación entre ambas entidades.

Métodos: Sobre una muestra de 57 sujetos, de los que 33 presentan demencia (casos) y 24 no (controles) se realiza estudio analítico a fin de establecer el grado de asociación entre la enfermedad de Alzheimer (EA) y la degeneración macular asociada a la edad (DMAE). Para ello, tras realizar anamnesis a todos los sujetos, se estudia el fondo de ojo mediante cámara no midriática tipo Topcon TRV-50VT.

Resultados: De acuerdo a la hipótesis de trabajo planteada, aplicada la razón de productos cruzados o de disparidad (odds ratio) se obtuvo un resultado positivo que determina relación causa efecto, ya que el porcentaje de casos con DMAE (42,4%) es superior al de controles con DMAE (25%). Por otro lado mediante la Chi cuadrado de Pearson, aunque no se establecieron diferencias significativas, los datos obtenidos muestran protección en el grupo...
However, such a difference between both groups was not strongly supported.

Conclusions: We suggest that AD and ARMD may have common factors concerning etiology and pathogenesis. Our dataset did not allow us to show a significant relation between both disorders, which is likely due to sample size and/or to age differences in the two studied groups. Even so, we feel that the possibility of such an association is justified, and future surveys to test this possibility are warranted. (Arch Soc Esp Oftalmol 2006; 81: 73-78).

Key words: Alzheimer’s disease, age-related macular degeneration, neurodegeneration, retinal drusen.

INTRODUCTION

At present, dementias are the third cause of death after cardiovascular diseases and cancer, with Alzheimer’s disease (AD) being the most frequent dementia. These diseases constitute one of the most relevant social and health problems due to its social impact and non-reversible nature, lack of knowledge of risk factors, reduced margin for prevention and a rapid increase of prevalence in parallel with the increases in life expectancy in developed countries. On the other hand, dementias have a significant repercussion over the expenses they generate, which will grow exponentially with the development of the disease.

Age-related macular degeneration (ARMD), first described by Pagenstecher and Gente in 1876, usually begins expressing beyond age 60. Yellowish-white deposits (drusen) begin to be seen at the level of the eye fundus, which end up altering the coroid-retina interface affecting the irrigation of photoreceptors and, in many cases (depending on the type, confluence, size and location of the drusen vis-à-vis the fovea), can degenerate or evolve toward coroidal neovascularization (neovascular ARMD) or atrophy plaque (atrophy ARMD).

ARMD is the main cause of legal blindness in developed countries. Most studies (1,2) agree in that the risk of developing ARMD increases with age. The WHO (3) estimates that the population over 60 will double in the next 20 years.

Some authors (4-6) have attempted to associate AD and ARMD on the basis of genetic characteristics, because both processes are considered to be chronic neuro-degenerative disorders with common characteristics such as their relationship to aging, their unknown etiology and more specifically the presence of senile plaques (extra-cellular formations with an internal nucleus of Ab amyloid peptide fibres) both in the gray matter of the brain and the macula of the retina. In addition, at the histological level, AD exhibits neurofibrillar balls (aggregates of hyperphosphorilated TAU protein) together with other less specific alterations.

Although the etiology of both pathologies is not clearly established, it is known that their origin comprises multiple causes both due to genetic as well as acquired factors. Among the former (7-9) related to AD we find family history, early mutation of the amyloid precursor protein gene (APP) or preseniline 1 (PS1) or preseniline 2 (PS2), or the ApoE genotype (alleles E2, E3, E4), involved in cholesterol transport, with different actions because while the allele form E4 increases the risk of suffering AD, allele E2 seems to protect against the disease (8,9). In turn, acquired factors comprise age, female gender, hypercaloric diets rich in saturated fatty acids and obesity. In what concerns ARMD, risk factors related to its appearance include white race, old age, female gender, smoking habit, hypercholesterolemia, exposure to sunrays, light eyes, hypermetropy, previous cataract surgery as well as family history (table I).
Both AD and ARMD will have repercussions on the quality of life of the patient, increasing the risk of falling and of social isolation which in many cases will lead to clinically established depression.

As a working hypotheses, our aim is to establish the relationship between AD and ARMD on the basis of neuro-degenerative criteria, in order to establish a possible association between both pathologies allowing us to formulate early AD diagnostic criteria on the basis of the degenerative lesions of the eye fundus (ARMD).

**SUBJECTS, MATERIAL AND METHOD**

A non-experimental, retrospective analytical study is carried out on a non-probabilistic sample divided in two groups (cases and controls), one comprising 33 out-practice subjects (cases) who attend a center specialized in dependent people with a mean age of 79.58 years (SD ±8.05), of which 20 (60.6%) were women and 13 men (39.4%). The second group comprised 24 non-institutionalized individuals (controls) without known diagnostic for degenerative pathologies, mean age 71 (SD±5.78), of which 16 (66.7%) were women and 8 (33.3%) were men.

For the group of cases the inclusion criteria were being over 60, having a diagnosis of AD as per the NINCDS-ADRDA (10) and DSM-IVR criteria (11) or of ARMD as per Bird and Wisconsin (12), signing the informed consent form or, in case of incapacity, the person in charge of the patient, and having the willingness to participate in the study. The exclusion criteria were having slight-serious AD preventing the exploration or bilateral myosis (pupil with diameter below 2mm without light-motor reflex explaining it), in accordance with aging or use of medication.

A full clinical record was made, in some cases filled in with the assistance of a relative or care giver, to collect data related to exposure to the risk factors described for both pathologies as well as family and clinical-pathological antecedents, among other data. Subsequently, an eye fundus study was made, taking a 50º retinography centered on the macula of each eye with Topcon TRV-50VT non-midriatic camera.

As regards the control group, inclusion criteria were being over 60 and not having previous diagnosis of AD or ARMD.

The data were collected and analyzed in the SPSS statistics program, version 11.5 for Windows, utilizing Pearson’s (Odds ratio) chi-square statistical method for establishing the association between AD and ARMD.

**RESULTS**

Of the 33 subjects assigned to the case group, 28 (84.8%) had a diagnosis of Alzheimer-type dementia and 5 (15.2%) other dementias. Fourteen (42.4%) had ARMD, of which 12 (36.6%) also had AD. In the control group, only 6 (24%) had ARMD.

Taking into account the risk factors in each pathology of the case group, 60.71% of subjects with diagnosis of dementia exhibited high arterial pressure and 64.28% had high cholesterol levels in blood. Among the subjects with ARMD, 60% referred to exposure to sunlight, 70% high arterial pressure, 40% had light-colored eyes and 35% had gone through cataract surgery. It is noteworthy that 95% of this group had high cholesterol levels in blood.

A joint assessment of the associated factors in both pathologies (AD-ARMD) revealed that in 66.7% of the sample there was exposure to sunlight and 41.7% previous cataract surgery. High arterial pressure appeared in 75% of cases, and high cholesterol levels in 91.7%.

Finally and according to the working hypothesis, a positive result was obtained to determine a cause-effect relationship (Odds ratio). The contingency table (table II) shows that the percentage of the «cases» group which ARMD (42.4%) is above that of the «control» group which also had ARMD (25%).

| Table I. Risk factors involved in each of the studied pathologies. AD and ARMD |
|----------------------------------|-----|-----|
| AD | Risk factors | ARMD |
|----------------------------------|-----|-----|
| Family history | Family history |   |
| Age | Age |   |
| Female gender | Female gender |   |
| White race | White race |   |
| Cardiovascular disease (HTA) | Cardiovascular disease (HTA) |   |
| Hypercholesterolemia | Hypercholesterolemia |   |
| Smoking | Smoking |   |
| Depression | Exposure to sun rays |   |
| Amyloid precursor protein | Light eyes |   |
| Apoe E4 Genotype | Previous cataract surgery |   |
On the other hand, with Pearson’s chi square (even though it does not establish significant differences) by applying Fisher’s exact statistics we obtain an exact bilateral AD-ARMD significance of 0.649, which indicates protection in the control group. This difference may be true in accordance with the hypothesis or can be erroneous in accordance with the difference between the ages of the control and experimental groups.

**DISCUSSION**

In what concerns the risk factors for developing AD as well as ARMD, some authors (13-15) consider tobacco, although in our study this relationship does not appear, neither does it appear in relationship to light-colored eyes. However, there is a coincidence with other authors (16-19) between high cholesterol and both pathologies, with Apo E being responsible as the protein which transports cholesterol (20); in addition, we also agree with them about the presence of other risk factors such as high arterial pressure, ischemic cardiopathy and exposure to sun rays for both pathologies. The relationship of ARMD with sun exposure and previous cataract surgery is directly proportional (21, 22).

Different studies (13, 15, 16) observed that the neuro-degenerative action of arteriosclerosis is enhanced by tobacco. Arteriosclerosis (20, 23, 24) causes a thickening of Bruch’s membrane in ARMD and an increase in amyloid angiopathy in AD, which determine a reduction of blood flow and endothelial damage (25), while tobacco causes neuro-toxicity through a reduction in the supply of oxygen to tissues.

Rotterdam’s study (16) describes allele E4 of Apo Lipoprotein E as being associated to both neuro-degenerative disorders, but in an opposite manner, which means that it seems to protect against ARMD (26, 27) but not from AD (28, 29). The presence of this opposition reduces the probabilities of E genotype apolipoprotein contributing to establish an association between ARMD and AD, and other common neuro-degenerative pathogenic factors will have to be determined.

Rotterdam’s study (16) calculated the prevalence of AD for successive stages of macular degeneration, observing a direct relationship with a high risk of prevalence of the subsequent development of AD in ARMD stages 3 and 4. In turn, Blanks (17, 30) compared retinae of elderly population with and without AD, considering the number of cells of the ganglion layer, their distribution, density, central projections and physiological properties, observing the early retina defects in the Alzheimer population.

Johnson (18), justifies the relationship between AD and ARMD establishing that the druse deposits contain a variety of immunomodulator molecules which unleash local inflammatory events and activate the supplement cascade, leading to degeneration of the photoreceptor cells. It is proposed that this chronic inflammatory process is the most important primary pathogenic element of ARMD. b-amyloid is involved as the main trigger because it forms a structural part of the vessel component inside the druse. This supplement activation process gives rise to an atrophy of the retina’s pigmented epithelium, the generation of druses and the pathogenicity of ARMD.

Anderson (6, 19) demonstrates that the genetics of apolipoprotein E4 is linked to AD as well as to ARMD, establishing a relationship of protection by apolipoprotein E4 for exudative ARMD but of risk for AD. This makes it necessary to search for other common pathogenic factors. In addition, the accumulation of druses in the macula is the most important risk factor for developing ARMD. The results of their studies show that the cellular remainders derived from the retina’s pigmented epithelium cells, deposited between the basal plate thereof and Bruch’s membrane, contribute to a chronic inflammatory response and subsequent formation of druses, thus agreeing with other authors (31). This fact could lead to the loss of progressive sight in the central portion of the macula. There are results which support local inflammation as playing an important role in the generation of druses and suggest that this process is similar to that of other age-related disorders such as AD and arteriosclerosis.

The functional relationship between druses and ARMD has been (and continues to be) controversial because on the one hand it is considered that the
formation of druses is a normal process in aging, while on the other hand it is established that said formation constitutes an early stage of atrophic or exudative macular degeneration. Many of the protein accumulations associated to druses have been identified as responsible for the pathogeny of other diseases such as AD, arteriosclerosis and amyloidosis (32), opening the possibility of common origins. Apo E is a cholesterol-transporting protein which is present in hard and soft druses (6,33); in the brain, one of the functions of Apo E is the regulation of cholesterol during the neuronal remodeling process. The genetics of apolipoprotein allele E is involved in the pathogeny of arteriosclerosis and AD (34), with reduced risk for exudative ARMD.

Accordingly, there is sufficient evidence to believe that AD and ARMD share ethiological and pathogenic factors and, even though our study was unable to establish a significant relationship between both pathologies, possibly due to the size of the sample or the age differences between both groups, we believe that the association is established, thus allowing for further work to establish said significance and therefore opening a new field of research utilizing retinal degeneration criteria as prognosis for Alzheimer-type dementias.

REFERENCES

1. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1992; 99: 933-943.
2. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1997; 104: 7-21.
3. Dentiche T, Milam AH, Lee VM, Trojanowski JQ, Dunaeif JL. Amyloid-beta is found in drusen from some age-related macular degeneration retinas, but not in drusen from normal retinas. Mol Vis 2003; 9: 184-190.
4. Vingerling JR, Dielemans I, Hofman A, Mullins RF, Hugenholtz VH, van den Brandt PA, de Jong PT. Is age-related maculopathy associated with Alzheimer’s disease? The Rotterdam Study. Lancet 1998; 351: 1840-1843.
5. Ott A, Slooter AJ, Hofman A, van Harckamp F, Witteman JC, Van Broeckhoven C, et al. Smoking and risk of dementia and Alzheimer’s disease in a population-based cohort study: the Rotterdam Study. Lancet 1998; 351: 1840-1843.
6. Klaver CC, Ott A, Hofman A, Assink JJ, Breteler MM, de Jong PT. Is age-related maculopathy associated with Alzheimer’s disease? The Rotterdam Study. Am J Epidemiol 1999; 150: 963-968.
7. Blanks JC, Torigoe Y, Hinton DR, Blanks RH. Retinal degeneration in the macula of patients with Alzheimer’s disease. Ann N Y Acad Sci 1991; 640: 179-180.
8. Johnson LV, Leitner WP, Rivest AJ, Staples MK, Radeke MJ, Anderson DH. The Alzheimer’s A beta-peptide is deposited at sites of complement activation in pathologic deposits associated with aging and age-related macular degeneration. Proc Natl Acad Sci USA 2002; 99: 11830-11835.
9. Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. Am J Ophthalmol 2002; 134: 411-431.
10. Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harckamp F, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer’s disease in the Rotterdam Study. Lancet 1997; 349: 151-154.
11. Hyman I, Schapar AP, He Q, Leske M, Hypertension, cardiovascular disease, and age-related macular degeneration. Arch Ophthalmol 2000; 118: 351-358.
22. Hirvela H, Luukinen H, Laara E, Sc L, Laatikainen L. Risk factors of age-related maculopathy in a population 70 years of age or older. Ophthalmology 1996; 103: 871-878.

23. Vingerling JR, Dielemans I, Bots ML, Hofman A, Grobbee DE, Jong PTV. Age-related macular degeneration is associated with atherosclerosis. The Rotterdam Study. Am J Epidemiol 1995; 142: 404-409.

24. Pauleikhoff D, Chen JC, Chisholm IH, Bird AC. Choroidal perfusion abnormality with age-related Bruch’s membrane change. Am J Ophthalmol 1990; 109: 211-217.

25. Ellis RJ, Olicchey JM, Thal LJ, Mirra SS, Morris JC, Beekly D, et al. Cerebral amyloid angiopathy in the brains of patients with Alzheimer’s disease: the CERAD experience, Part XV. Neurology 1996; 46: 1592-1596.

26. Souied EH, Benlian P, Amouyel P, Feingold J, Lagarde JP, Munnich A, et al. The epsilon 4 allele of the apolipoprotein e gene as a potential protective factor for exudative age-related macular degeneration. Am J Ophthalmol 1998; 125: 353-359.

27. Ott A, Breteler MM, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. Am J Epidemiol 1998; 147: 574-580.

28. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 1993; 90: 1977-1981.

29. Tsai MS, Tangalos EG, Petersen RC, Smith GE, Schaib DJ, Kokmen E, et al. Apolipoprotein E: risk factor for Alzheimer disease. Am J Hum Genet 1994; 54: 643-649.

30. Blanks JC, Hinton DR, Sadun AA, Miller CA. Retinal ganglion cell degeneration in Alzheimer’s disease. Brain Res 1989; 501: 364-372.

31. Penfold PL, Madigan MC, Gillies MC, Provis JM. Immunological and aetiological aspects of macular degeneration. Prog Retin Eye Res 2001; 20: 385-414.

32. Mullins RF, Russell SR, Anderson DH, Hageman GS. Drugs associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. FASEB J. 2000; 14: 835-846.

33. Klaver CC, Kliffen M, van Duijn V, Hofman A, Cruts M, Grobbee DE, et al. Genetic association of apolipoprotein E with age-related macular degeneration. Am J Hum Genet 1998; 63: 200-206.

34. Davignon J, Cohn JS, Mabile L, Bernier L. Apolipoprotein E and atherosclerosis: insight from animal and human studies. Clin Chim Acta 1999; 286: 115-143.