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Radiotherapy-induced changes in high-density lipoproteins: implications for alzheimer's disease and oncology

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ABSTRACT

High-Density Lipoproteins (HDL) have an important role in the balance of cholesterol in the human body. Especially Apoliprotein E (APOE) the E4 allele, which is a major risk factor of Alzheimer's disease, yet we must not forget the fact that it is a major protein with a strong affinity for High-Density Lipoprotein (HDL), as it is involved in the transport of lipids in both the peripheral and central nervous systems of the body. So, the aim must be defined, which is to determine the effect of the APOE genotype on HDL function Volume in the context of Alzheimer's disease. This case-control study includes 114 subjects, 60 controls and 54 patients to fulfill the aim of study. High-density lipoproteins are one of the elements that cause cognitive impairment and Alzheimer's so that, calculation and measurement of Cholesterol Efflux Capacity (CEC) as well as Lecithin and Cholesterol Acyltransferase (LCAT) activity were done, in addition to the neurological and psychological tests in order to classify the type of dementia, magnetic resonance imaging have used to determine whether cognition is related to HDL function and size. Results showed the predominance of the ε3 allele in the sick group with frequency of the aisle ε4 in our study is twice as high in the sick group (27.80%) as in the control group (12.3%) showing a variation of 15.5%; it reaches a peak in the age group of 70years-79 years.

Because the size of HDL plays an important role in determining the degree of disease and how to fight it. As all evidence indicates that High-Density Lipoprotein (HDL) particles in the Central Nervous System (CNS) and afferents are the main etiology of Alzheimer's disease.

We were able to determine whether HDL CEC and LCAT activity were altered within a large group of APOE genetic proteins.

Keywords: alzheimer's disease, APOE, cholesterol efflux capacity, HDL, CNS, oncology, radiotherapy-induced changes

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INTRODUCTION

One of the most serious brain conditions affecting senior people is Alzheimer's disease. A significant public health issue is emerging from a condition that is both undertreated and under recognized. An effort that has been progressively growing over the past ten years has been made to identify the disease's genesis and create pharmaceutical treatments. Improved clinical diagnostic standards and better behavioral and cognitive disturbance treatment are recent breakthroughs [1].

Alzheimer's Disease (AD) is a fatal neurological condition that accounts for 50%–75% of all dementia types. The number of people with AD or a related dementia who received a diagnosis in 2015 was projected to be around 44 million worldwide. There are 4.6 million new cases of dementia recorded annually, and by 2030, there will be roughly twice as many AD patients. Several differ-ences in the likelihood of developing AD may be explained by genetic variables, particularly in familial AD and Early-Onset AD (EOAD), where the majority of genetic variants are linked to the processing of amyloid-(A) [2].

In sporadic late forms, more frequent (approximately 70% of the cases) numerous genetic factors and environmental factors act alone or in synergy, probably inducing susceptibility individual to the development of these forms [2,3].

Numerous studies have shown that the ε4 allele of Apo E is a factor of risk for this disease and there would be a relationship between the number of ε4 alleles and incidence of AD, the risk of developing the disease is multiplied by 3 for a heterozygote and by 8 for a homozygote ε4 [2,3].

The potential pathogenicity of the Apo E ε4 allele is complex. Many hypotheses are currently proposed to explain it, apart from a direct action of APOE on the formation of amyloid deposits; many other hypotheses have been formulated. They are based on lipid metabolism, the development of an inflammatory response or even a specific toxicity of the products of the metabolism of APOE [4].

The symptoms and evolution of the disease: The disease always begins with an asymptomatic phase that can last longer of 20 years, as it affects regions of the brain, it will cause the loss of certain functions or skills. The onset is insidious; marked by the

gradual onset of memory disorders, phasic, problems of praxis and gnosis as well as impairment of the function's executives [5].

The average duration of its evolution from 5 years to 9 years, in the long term; the disease causes deterioration in general condition. Eating disorders and difficulties swallowing are often the cause of significant weight loss with impaired immune defenses. This pro-motes infectious complications which are often cause of death. Apolipoprotein E next to the genes which intervene within the framework of autosomal forms dominant of AD a fourth gene has been identified, which acts as a risk factor of the disease. This is the Apolipoprotein E (APO E) gene. The Apo E gene is located at the centromere end of an entire family of genes encoding the Apoli·poprotein group E, CI, and CII, on chromosome 19, in the region q13.2. This 3.7 kb gene encoding an mRNA that is 1163 base pairs long has four exons and three introns. The sizes of the exons from the 5' end towards the 3 'end are respectively 44,66,193 and 860 nucleotides, those of the introns are 760, 1092 and 582 nucleotides. The first exon is non-coding, the second exon codes for a signal peptide (18 amino acids), the third exon for the first 61 amino acids and fourth for mostly mature protein.

Polymethyl Methacrylate (PMMA) and Aluminium respectively. According to the manufacturer's instruction, the working voltage of both of the dosimeters was 400 V (Figure 1).

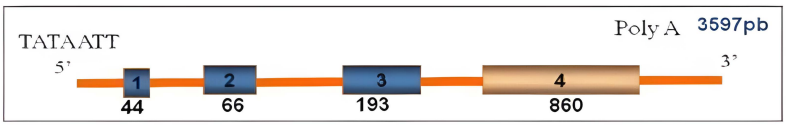

Fig. 1. Apo E gene Alzheimer's Association. (2021) Alzheimer's disease Facts and Figures

Apo E is cleaved by a peptidase for the 18 amino acids making up the peptide signal, when passing through the membrane of the endoplasmic reticulum, the apoE intracellular undergoes O-glyco-sylation's, accompanied by sialylation which takes place at a single Apo E site, to threonine 194 [6, 7].

The protein is then secreted and desalinated extracellular. 90% of the plasma Apo E is desalinated. mature apo E secreted is a protein with an apparent molecular weight of 34 kDa (299 amino acids). The amino acid substitutions at positions 112 and 158 of the three main Apo E isoforms induce isoelectric point changes (apo E2, pI=5.4; apo E3, pI=5.2; apo E4, pI=5.4) [8].

PATIENTS AND METHODS

The study was focused on two types of population: 1 control group and population of 2 patients.

Alzheimer's disease is diagnosed and affects both sexes. Patients were recruited and selected from several departments, such as the city's neurology department and the specialist counseling department, which means that we divided them into groups: Healthy subjects of both sexes were over 60 years old [3, 9].

Inclusion and exclusion criteria were established for patients: Inclusion criteria: Subjects with the potential or likelihood of retain-ing AD at a service level Neurology at the city's university hospi-tal. The diagnostic criteria for recruiting patients are those of the DSM IV (diagnosis and Statistical Manual of Mental Disorders Fourth Edition), those of the NINCDS-ADRDA (National Insti-tute of Neurological and Communication Disorders, Stroke, and Alzheimer's Disease Society for Diseases and Related Disorders), as well as the MMSE (Mini Mental status check) [4, 9].

The samples were taken from subjects fasting for at least ten hours, for performing a lipid profile. The recommended blood sample for DNA extraction requires the use tubes with an EDTA anticoagulant which is a chelator or an inhibitor of the action of DNase or nuclease enzymes [8].
The diagnosis of probable or possible Alzheimer's disease is confirmed for each patient by the neurologist. All subjects underwent a cognitive evaluation via the modified MMSE test (Appendix 4), a score is assigned for each patient. An interrogation of the patient is carried out by ourselves or by the consultant doctor [10].

All samples are carefully labeled and the blood collected is sent directly to the laboratory for analysis. The dosage of the various lipid parameters was carried out in the manner next: Methods for determination of lipid parameters: Cholesterol, triglycerides and HDL cholesterol were measured on the same day Cholesterol test: Cholesterol can be measured in different ways, the oldest being Colorimetry, currently all laboratories use enzymatic methods in our study, cholesterol was measured by an enzymatic method (Trinder reaction) by automatic analyzer (technicon RA and Opera systems [11].

The intensity of the coloring of the quinone imine measured at 500 nm, is directly proportional to the amount of cholesterol present in the serum sample [12-15].

STATISTICAL ANALYSIS

The results of all the samples obtained as well as all the parameters considered were processed by Epi info version 6.0 software. Different methods, as well as different tests were used in this study. Equality of variances is the basic condition for comparison tests of averages [16].

This is the ANOVA test. We therefore used ANOVA in the case of a normal distribution. In the case where the different variances, objectified thanks to the Bartlett variance homogeneity test, we used the Mann-Whitney non-parametric test [15].

RESULTS AND DISCUSSION

Distribution of subjects according to pathology and gender: This case-control study includes 114 subjects including 60 controls and 54 patients fulfilling the diagnostic criteria for probable M.A. Distributed as follows: [17, 18]

- 60 Witnesses including 30 Women and 30 Men.
- 54 M.A including 25 Women and 29 Men.

Tab. 1. Distribution of subjects according to pathology and sex

	F	M	Total
ALZ	25	29	54
Witnesses	30	30	60
Total	55	59	114

The (Table 1) illustrated that, there is no predominance of one sex over one. Otherwise, this result does not agree with most of the data in the literature. According to several studies, women have a higher risk of developing Alzheimer's disease than men. In the Piqued study, the incidence of Alzheimer's disease was, before the age of 80, higher in men than in women. women, while the reverse is true after 80 [19].

Biological and hormonal differences, including a possible effect of estrogen could explain this difference in the incidence according to sex. Several studies have shown that taking hormone replacement therapy for menopause appeared to be associated with a more than 50% reduction in disease risk of Alzheimer's [20].

Life expectancy, higher for women than for men, could also explain the observation. It should be noted that in some countries such as the United States where this gap in expectation of life between men and women is less, the incidence of Alzheimer's disease does not vary by gender [21, 15].

Patients and controls are categorized as 10 years old except those Over 90 and they are all categorized at once.

Tab. 2. Distribution of patients and controls by age group

	ALZ	Witnesses
50-59	4	18
60-69	11	17
70-79	29	16
80-89	9	7
≥ 90	1	2

The Table 2 shows a prevalence of AD of around 7% in the population aged under 65; it increases with age, more than half (54%) of our patients found in the 70-79 (years) age group, followed by the 60-69 (years) and 80-89 (years) age group with rates of 20.37%. The average age of AD subjects is 73.47 ± 7.61, slightly higher than that of controls which is 67.17 ± 10.84 (Figure 2)[22].

Tab. 3. Average ages in the sick and control groups

	F	M	Averages
ALZ	74,68 ± 6,7	72,4 ± 8,29	73,47 ± 7,61
Witnesses	68,26 ± 12,2	66 ± 9,27	67,17 ± 10,84

Age is undoubtedly the main risk factor for AD, which does not appear as long as the person has not reached a minimum adult age, generally 65 years old. As shown in the Table 3, age seems to be linked to an exponential increase in frequency of the disease; it reaches a peak in the age group of 70-79 (years) [18, 22].

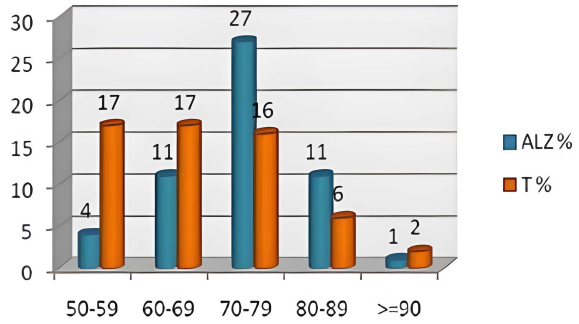

Fig. 2. Distribution of patients and controls by age group

In agreement with most studies that the incidence of AD practically doubles by age group of 5 years after 65 years, so that the increase in prevalence as a function of age is less rapid after 90 years. Some studies suggest that a plateau could be reached for the oldest age groups [23].

These assumptions; suggesting that, past a certain age, this growth exponential would stabilize, remain to be discussed, insofar as, beyond the age of 85, the study numbers are low In the European cooperative study, the EURODEM research group has gathered the results obtained between 1980 and 1990, on 8 cohorts of subjects over 65.

GENETIC STUDY OF APOE

The genetic study of the polymorphism of Apo E concerned the 60 controls and 54 patients [24].

Tab. 4. Apo E allele frequencies in control and disease

	ε2		ε3		ε4	
	N	%	N	%	N	%
Witnesses	3	4.9	50	82.8	7	12.3
ALZ	2	4.6	36	67.6	16	27.8

ompatible with a recent study on the population of Constantine which shows the predominance of the APOE ε3 allele gene [25]. This trend, compared with data from the literature, shows that it is similar to the results presented by studies, French, Spanish, Italian, Finnish, and on Moroccan and Tunisian populations [12, 16, 24].

Result illustrates that, the frequency of the ε4 allele is 27.80% twice that of in the sick group compared to the control group (12.3%), which represents a difference 15.5%. Its increase is the result of a decrease in the allele frequency ε2 and 3 In the M group [15, 24].

The frequency of the ε4 allele is increased in the late forms of AD β Various European countries, the United States and Japan. in all these Studies of the frequency of ε4 range from 0.10 to 0.18 in the general population, whereas it increases significantly between 0.24 and 0.52 in subjects with Alzheimer's disease [25] (Table 4).

THE GENOTYPIC FREQUENCIES OF APO E

The Table 5 shows the comparison of genotypic frequencies between controls and Alzheimer's subjects [26].

Tab. 5. Distribution of genotypic frequencies in the two groups

	Witnesses		ALZ	
	n	%	N	%
ε3/ε3	42	68,9	26	48,1
ε3/ε4	12	19,7	19	35,2
ε2/ε3	5	8,2	2	3.7
ε2/ε4	1	1.6	3	5.6
ε4/ε3	1	1.6	4	7.4
Total	61	100	54	100

The genotypic distribution of this gene indicates that ε3/ε3 is the dominant genotype in the control group and in the sick group, with a frequency of 68.9% and 48.1% respectively, these results agree with those found in all the studies carried out worldwide.
In the control group the ε3/ε3 genotype and followed by the ε4/ε3 genotypes (19.7%) and e2/e3 8.2%; whereas the ε2 / ε4 and ε4 / ε4 genotypes are only present in 3.2% of the all of the witnesses. On the other hand, in the sick group, the genotypic frequencies show a descending order different from that of the controls, the most frequent ε3/ε3 genotype, followed ε3/ε4 (35.2%), ε4/ε4 (7.4%), ε2/ε4 (45.6%) and e2/e3 (3.7%) genotypes. We note that the ε3/ε4 genotype is more frequent in the sick group, it is increased by 15.7% compared to controls. The ε4/ε4 genotype is also more significant in patients, it is increased by 5.8%. Likewise, the genotype ε2/ε4 and more important in patients.

While in the two groups no carriers of the genotype ε2/ε2; however, carriers of the ε2/ε3 genotype are more numerous in the group controls than in the sick group. We note that the number of patients increases with the presence of the ε4 allele, thus, only 3.7% of patients have ε2/ε3 genotypes, while 48% present at least a single copy of ε4, suggesting an association between this allele and the MY. Our results are consistent with all studies, demonstrating an association direct or indirect apoE polymorphism with AD in different group's ethnicities around the world. The study results agree with those of Alan Roses et al, 1993 which were the first to suggest that the e4 allele had a strong association with Alzheimer's disease [27-29].

Schmeichel D. showed that the frequency of the e4 allele reached 40% in a population of patients with late familial forms of the disease. This association has been confirmed by many clinical studies and epidemiological, extended to late sporadic forms as well as certain forms early [30].

CONCLUSION

1. The Apolipoprotein E gene is the only genetic susceptibility factor recognized; the first study carried out in 1993 showed that the frequency of the ε4 allele reached 40% in a population of patients with late familial forms of illness. Since then, this association has been confirmed by numerous studies, extended late sporadic forms as well as some early forms and finally supplemented by the demonstration of a protective effect of the e2 allele. In the present study, the allele frequencies were determined on a sample of 114 people divided into 2 groups. A group of 60 age witnesses average of 67.17, and 54 patients fulfilling the diagnostic criteria for probable AD, average age of 73.47.
2. The predominance of the ε3 allele in the control group and the sick group with frequencies of 82.8% and 67.6% respectively. This trend is consistent with results found in other populations. The frequency of the aisle ε 4 in our study is twice as high in the sick group (27.80%) as in the control group (12.3%) showing a variation of 15.5%. In Western Europe, the frequency of ε4 in AD groups and in the general population follows a gradient decreasing north-south from northern countries with prevalence's of 0.2, to a prevalence of 0.1 in the countries of the Mediterranean basin (Spain and Italy).
3. The Studies have shown that subjects carrying a ε4 allele would have a relative risk of AD of 1.84 and homozygous ε4 subjects a risk of 3.3 compared to subjects who do not carry

this allele. This pattern appears in research results with ORs of 3.23 in e4/e4 homozygous subjects and ORs of 2.56 in heterozygous ε3/ ε4. On the other hand, the protective role of this ε2 allele in the disease is not obvious and remains to be demonstrated.

4. The results reveal a slight increase in the levels of TC, LDL, and a slight decrease in HDL levels in patients compared to controls.

Those results agree with some studies carried out around the world, but the arguments proving the link between the serum lipid profile and Alzheimer's disease are still fragmentary and controversial. This study examined the association between disease and other risk factors. risk, hypertension, diabetes, level of study, history of head trauma, alcohol consumption and smoking.

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