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Review Article

Genetic Influences on Alcoholism in Older Adults: A Marker-Based Approach

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Abstract

Alcoholism is a common but little-recognized problem among the elderly. Two-thirds of alcoholics are known to age with the medical and psychosocial sequelae of early-onset alcoholism. The definitions for alcohol abuse and dependence may not apply as easily to older people. Older adults are a heterogeneous group, and risky drinking can be difficult to recognize. Describe the genetic markers and alcoholism in older adults. A bibliographic search was conducted in the ScienceDirect, PubMed, WHO information, and geriatric guidelines databases. The following search terms were used: addictions in the elderly, alcoholism in the elderly, and genetic markers of addictions in the elderly in Spanish and English. Alcohol abuse may be an underestimated problem among aging people. The relationship between alcohol consumption, risk factors, consequences, and reasons for consumption must be studied from different perspectives. Genetic factors show significant evidence of a distinct susceptibility to the development of alcoholism. Research focused on genetic aspects will help to clarify the central mechanisms involved in alcoholism. It is necessary to establish prevention and treatment strategies in older adults with alcoholism that prevent medical complications.

Keywords: Older Adult; Alcoholism; Genetic Markers; Addiction; Aging

Introduction

Alcoholism is a common disorder of complex origin, as individuals react discordantly when exposed to different amounts of alcohol. Several epidemiological, biomedical and psychosocial investigations have found serious adverse effects in people after alcohol consumption. Physiological, sociocultural and psychological factors may play a relevant role in determining this disease's thresholds and lifetime prevalence [1]. In fact, social restrictions have been shown to have a major influence on the risk of alcohol dependence, particularly in societies with a high prevalence of alcoholism [2].

Between 2015 and 2050, the percentage of older adults worldwide will increase from 12% to 22%, and by 2025, 80% of older adults will be in Latin American countries. Although epidemiological studies have shown a decrease in alcohol consumption as people get older, the number of older adults who drink alcohol is increasing [3]. Alcohol consumption is a complex phenomenon related to lifestyle, gender, drinking history, social patterns, physiology, cultural heritage, health condition, drinking norms and moral principles [4]. Alcohol consumption plays a significant role in the lives of the elderly, and there are reasons to assume that this role will become increasingly prominent in

the future as baby boomers age. Furthermore, the relationships between alcohol consumption and risk factors, its harmful consequences, as well as the motives and subjective reasons for alcohol consumption should be studied from several different perspectives [5].

The use of genetic markers allows the identification of genetic diversity among people with alcoholism. The clinical diagnosis of alcoholism is based on standardized criteria in the Diagnostic and Statistical Manual of Mental Disorders. Currently, the relevant genes present in people with alcoholism are those encoding enzymes involved in ethanol metabolism and those whose product is related to the neurological pathways of alcohol addiction. Several authors claim that there is no main gene that causes alcoholism, but rather it is considered that it is the interaction of several genes that manifests itself in this disease and that each of them interacts under the influence of the environment [6].

Materials and Methods

A systematic electronic search of articles was carried out in accordance with the PRISMA 2020 guidelines statement. The search was conducted from different references found in databases such as PubMed, VHL, BBO, information from the World Health Organization, geriatric guidelines, scientific articles and official documents on the topics of aging, addictions, alcoholism and elderly people, and the genetics of addictions.

The following inclusion criteria were used: a) studies conducted from 2000 to 2022; b) participants: older adults; c) type of study: quantitative; d) study design: cohort, longitudinal, transversal; e) language: Spanish and English; f) phenomenon to be reviewed: alcoholism, genetic markers, and elderly people. The search terms used were: "addictions in older adults", "alcoholism in the elderly", "genetic markers of addictions in older adults" in Spanish and English. The search strategy was used in the same way in all reported databases.

The evaluation method was additionally based on meeting the inclusion criteria of the SPIDER methodology, a) sample (S): Scientific articles; b) phenomenon of interest (PI): Older Adults, Alcoholism and Genetic Markers; c) study design (D): Non-experimental; d) evaluation (E): Knowledge; e) Type of study (R): Quantitative. This article presents two sections in accordance with the state of the art: alcoholism in older adults and associated genetic factors.

Alcoholism in the elderly

From 2002 onwards, among persons aged 65 years or older, the estimated prevalence for alcohol abuse is 12% and for alcohol dependence 24% [7]. Hazardous drinking is more common among older adults with alcohol use disorders and is likely to be responsible for much of the damage to the health and well-being of older adults. Prevalence rates of hazardous drinking in them (defined as more than 3 drinks on one occasion or more than 7 drinks per week) are estimated to be 16% for men and 11% for women [8].

There is also a substantial proportion of the elderly population who are binge drinkers (defined as 5 or more drinks in a day). Rates of binge drinking in older adults are 19.6% for men and 6.3% for women according to data from the 2005-2006 National Survey on Drug Use and Health. In a study of community-dwelling older adults who reported having one or more drinks in the previous 3 months, 67% reported binge drinking in the past year [9].

Evidence from studies in identical twins supports a genetic component associated with alcohol use or substance dependence [10], and genome-wide association studies have identified dozens of variants that contribute to the risk of developing chronic alcohol use, making it important to identify these markers in older adults [11].

Associated genetic factors

Genetic factors are associated with various alcohol consumption phenotypes. Gene association studies have provided information regarding the role of cholecystokinin [12] in alcoholism [13,14]. A novel finding in the genome-wide alcohol-related study is that genes of African descent, such as MaxAlc, significantly correlate with the *B4GALT1* gene on chromosome 9 [12]. The *B4GALT1* gene is a member of the galactosyltransferase gene family and encodes an enzyme related to glycoconjugate and lactose biosynthesis. The metabolism of glycoconjugates that occurs in the liver is altered in the presence of chronic alcohol consumption, and glycoconjugate-related biomarkers are considered markers of excessive alcohol

consumption [15]. Current research makes it clear how genetic factors are expressed in an important way for the development of alcoholism [16]; and polymorphisms of the genes encoding the main enzymatic systems that intervene in the hepatic metabolism of ethanol through the action of three enzymes have been identified; the enzyme alcohol dehydrogenase (ADH), the enzyme aldehyde dehydrogenase (ALDH) and the enzyme cytochrome P450IIE1 (CYP2E1) [12].

The concentration of ethanol in the blood after the ingestion of alcoholic beverages strictly depends on its pharmacokinetics, which determines the dose to target organs and the pharmacodynamic responses of ethanol. After oral administration, alcohol is readily absorbed from the gastrointestinal tract. Its absorption takes place by passive diffusion, 20% through the stomach wall, the remaining 80% is absorbed through the duodenum and small intestine. The absorption rate varies with the time of day, dosage form, concentration and consumption pattern, mainly related to the state of gastric emptying [17].

In the cytosol of hepatocytes, ethanol is oxidized to acetaldehyde, in a reversible reaction catalyzed by class I ADH, which becomes saturated after only a few drinks. Acetaldehyde is then oxidized in an irreversible reaction to acetate, by the mitochondrial form of ALDH. Since the enzyme has a very low Km, the removal of acetaldehyde is very efficient, so that the highly toxic ethanol oxidation product is eliminated soon after its formation. It has been calculated that during ethanol intoxication only 1-2% of the acetaldehyde formed in the liver enters the bloodstream, resulting in negligible levels [18].

The enzyme alcohol dehydrogenase (ADH) is a cytosolic protein capable of metabolizing ethanol and a wide variety of substrates, including other aliphatic alcohols, hydroxysteroids, and the products of lipid peroxidation. ADH exists as a polygenic family of seven genes located on chromosome 4, translated into various forms of human ADH. These can be divided into five main classes or distinct groups, according to their subunit composition as well as their physicochemical properties [19].

Human ADH is a dimeric protein, resulting from the association of different subunits with a molecular weight of 40 kD each. Class I ADH (ADH1, ADH2 and ADH3) consists of isoenzymes formed by different combinations of subunits (α, β, γ), encoded by genes either from the same locus or from different loci. Homodimeric proteins are composed of identical subunits encoded by the same locus, whereas heterodimeric proteins are composed of alleles encoded from different loci (e.g., αβ, αγ) or from different alleles at the same locus (e.g., β1β2, γ1γ2). Although 20 ADH isozymes are known, it has been suggested that ADH variants may be involved in different attitudes to alcoholism, since allele frequencies differ between alcoholics and controls [20].

The ADH2 gene can be present as ADH2*1, ADH2*2 and ADH2*3, encoding the β1, β2, and β3 subunits, respectively, which differ by single nucleotide exchanges, however, the difference of a single amino acid in the protein determines very different catalytic properties. The enzyme containing the β1 subunit has high affinity and low ethanol capacity, whereas the β2 and β3 forms show lower affinity and higher capacity. The Vmax of β2 homodimers is about 40 times higher than that of β1 homodimers. As a consequence, the activities related to the β2 and β3 subunits are not greatly limited by the ability to process large amounts of ingested ethanol [21].

Different tissues show uneven expression of the human ADH gene; the liver contains a large amount of ADH and expresses the largest number of isozymes, mainly class I. ADH5 (χ-ADH) is expressed in all human tissues tested to date, ADH4 (π-ADH) is the only one expressed in the liver, while ADH7 (σ-ADH) is the isoform that is only expressed at low levels in the liver [22]. However, it is present in significant amounts in gastrointestinal tissue, mainly in the gastric mucosa of Caucasians, but almost absent in Asians [23]. Similarly, low ADH activity has been demonstrated in the gastric mucosa of women of Caucasian origin [24]. This feature has been associated with a lower gastric first-pass effect on ethanol toxicokinetics observed in both Asian populations and women, as well as a decreased ethanol clearance and consequently an increase in blood alcohol levels that may contribute to the greater susceptibility of women to ethanol [25].

Regarding ALDHs, they are cytosolic enzymes expressed in a wide range of tissues. They differ in their electrophoretic mobility, kinetic properties, as well as in their cellular and tissue distribution. In addition, they show a certain degree of overlap and substrate specificity [26]. The genes encoding ALDH enzymes are divided into nine large families, the most important of which

are family 1 corresponding to cytosolic ALDHs (ALDH1), family 2 to mitochondrial ALDHs (ALDH2), and family 3 which groups the main constitutive and inducible ALDHs (ALDH3) found in human stomach, saliva and hepatocarcinoma [27,28]. Based on the kinetic properties, sequence similarities, and nomenclature of ALDH proteins, they have been classified as class I (low Km, cytosolic), class II (low Km, mitochondrial) [29], and class 3 [30]. There are multiple molecular forms of ALDH in human liver, but only the class I and class II isozymes, encoded by genes ALDH1 and ALDH2; whereas ALDH3 and ALDH4 show a lower affinity toward acetaldehyde and propionaldehyde as substrates [31].

The genetic factor that is most frequently significantly correlated with reduced ethanol consumption and the incidence of alcoholism is the polymorphism of the functional gene ALDH2. The enzyme is encoded by two distinct alleles on chromosome 6: ALDH2*1 and ALDH2*2, which differ by the substitution of glutamate to lysine at position 487 (E487K) due to a point mutation (G ⇒ A transition). Although the difference between the two alleles appears to be minimal, the proximity in primary structure between the mutation site and the region containing cysteine residues, most likely involved in the catalytic cycle, is consistent with the phenotypic decrease in ALDH2 activity, associated with the genotype variant [32].

In fact, individuals homozygous for the ALDH2*2 mutation completely lack ALDH2 activity, whereas heterozygous individuals display ALDH2*1,2. The genotype maintains between 30-50% of ALDH activity. Blood levels of acetaldehyde in ALDH2*2 homozygous individuals are 6-20 times higher than in ALDH2*1, in which acetaldehyde is hardly detectable after ethanol consumption. The blood concentrations of acetaldehyde reached in individuals homozygous for ALDH2*2 cause unpleasant side effects that protect them from alcoholism. However, heterozygous individuals can become heavy drinkers or even alcoholics, thus experiencing the toxic effects due to the production of acetaldehyde [33].

After ingestion of a small amount of alcohol, approximately 10% of ethanol is metabolized in the liver, with the help of the microsomal cytochrome P450 CYP2E1, which catalyzes its oxidation to acetaldehyde and then to acetate [34]. During the reaction, CYP2E1 generates reactive oxygen species (ROS), such as H2O2, superoxide anion, hydroxyl radicals and substrate derivative, which can cause oxidative stress, leading to lipid peroxidation, protein inactivation, increased cytokines and DNA damage leading to cell death [35]. In experimental models, where alcoholic disease is induced, an increase in the production of free radicals has been found, as well as a lower availability of antioxidants and/or alteration of the activity of several enzymatic systems capable of detoxifying ROS and their derived products, including the enzyme glutathione S-transferase (GST), the enzyme superoxide dismutase, glutathione peroxidase and catalase [36].

Potential sources of ROS in alcoholic disease are compartmentalized to microsomes, via CYP2E1 and cytochrome P450 reductase, mitochondria, via the electron transport chain, peroxisomes, via fatty acid oxidases, and in the cytosol, xanthine oxidase and the enzyme aldehyde oxidase. However, among all the potential sources of hepatic ROS, CYP2E1 has been the focus of attention for its pathogenic role in alcoholic liver disease [37]. In addition to ROS, 1-hydroxyethyl radicals produced by CYP2E1 during ethanol oxidation covalently bind to proteins forming products capable of inducing antibodies that have been found in alcoholic humans [38].

The CYP2E1 gene has been mapped to chromosome 10 and is composed of 9 introns and 8 exons, encoding a 493 amino acid protein. A tandem repeat was identified in the CYP2E1 regulatory region. The polymorphic CYP2E1*D has been associated with increased CYP2E1 inducibility and has been suggested to contribute to the development of alcohol and nicotine dependence. The CYP2E1*1D allele contains a repeat sequence in the 5' flanking region of the gene that may disrupt negative regulatory elements. Individuals homozygous and heterozygous for the CYP2E1*1D gene were found to have increased CYP2E1 activity after ethanol consumption [39]. Chronic ethanol consumption, leading to CYP2E1 induction, may result in increased conversion of known hepatotoxic agents to their toxic metabolites [40], possibly explaining the increased susceptibility of alcoholics to the adverse effects of industrial solvents [41]. Some evidence indicates that older adults who have been prenatally exposed to alcohol often suffer from mental disorders and maladaptive behaviors and are likely to become alcoholics [42,43].

Results and Discussion

Researching the genetic aspects of alcoholism in older adults is crucial to clarify the central mechanisms involved in this problem and to establish appropriate prevention and treatment strategies. This population has a higher rate of comorbid medical and psychiatric conditions. Moreover, the medications used to treat them create a complicated picture of unique risks and vulnerabilities. Even healthy levels of alcohol consumption established at a young age and then sustained into old age are a risk factor for health problems among older adults.

While social factors are relevant, such as lifestyle changes, bereavement, social isolation, loneliness and unemployment, which may influence alcohol consumption in this age group, exploring genetic factors associated with alcoholism in older adults is imperative.

Alcohol consumption in older adults has been insufficiently studied globally [44]. In Mexico, research on alcoholism in older people is insufficient. Although it is an age group considered a vulnerable population, there are not enough lines of research to address it in a holistic manner.

Older adults present a series of clinical conditions such as chronic degenerative diseases, sarcopenia, frailty, polypharmacy, disability, physical and economic dependence, as well as alterations in the social and psychological sphere that put their health at high risk. It is generally known that older adults do not stop taking their medication and combine it with alcohol. This behavior is worrying since it is a growing population group.

Several authors point out that it is feasible to closely index the genetic risk for alcohol dependence [45] by collecting quantitative data on alcohol consumption [46]. An important contribution that gene association studies have made to understanding the genetics of alcohol users is the finding that the genetic architecture of individuals with chronic alcoholism differs from that of individuals who consume alcohol only occasionally [47-49]. Genetic studies may help to understand the biological and medical consequences of habitual alcohol consumption.

Studies indicate that one in ten adults aged 81 to 90 years can be classified as alcoholics [50]. In addition, older adults are identified as a risk group for alcohol consumption where forgetting to take medication, falls or injuries, polypharmacy and complications associated with other diseases due to alcohol consumption are reported [51]. Genetic studies are needed to identify the genes involved in the development of chronic alcoholism.

Conclusion

Researching genetic factors associated with alcoholism in older adults is vital for understanding the underlying mechanisms of this complex disorder and for developing effective prevention and treatment strategies. As the population of older adults continues to grow, particularly in regions like Latin America, the prevalence of alcohol consumption within this demographic is increasing despite overall declines in drinking rates with age. This presents unique challenges, given that older adults often face multiple comorbid health conditions and may be more vulnerable to the adverse effects of alcohol, especially when combined with medications.

Moreover, while psychosocial factors such as isolation, lifestyle changes, and loss can significantly influence alcohol consumption patterns in older adults, it is equally important to explore the genetic predispositions that contribute to alcoholism. Evidence suggests that specific genetic markers related to alcohol metabolism and addiction pathways can provide insights into individual risks. Understanding these genetic influences can lead to more personalized and effective interventions.

Despite the risks, research on alcoholism in older adults remains limited, particularly in countries like Mexico. This gap highlights the need for comprehensive studies that consider both genetic and environmental factors to fully address the complexities of alcoholism in this vulnerable population. By advancing our knowledge in this area, we can better support older adults in maintaining their health and well-being as they age.

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Conflict of Interest

The authors declare no conflict of interest.

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