Association between alcohol and Alzheimer's disease (Review)

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disease characterized by dense deposition of amyloid-β (Aβ) protein in the brain, failure of the memory and dementia. At present, there is no cure for AD and current treatments only provide a temporary reduction of symptoms. Thus, there is a need for effective preventive/curative strategic approaches. Accordingly, epidemiological studies have reported a reduction in the prevalence of AD in individuals ingesting low amounts of alcohol, while a moderate consumption of ethanol may protect against Aβ. These data are conflicting with other observations that assigned detrimental effects of heavy alcohol use on brain function, which are apparently similar to those observed in AD. These discrepancies questioned whether or not alcohol is a protective agent against the development of AD, whether the probable protective effects are influenced by the quantity and/or frequency of drinking. These issues are addressed in this review with the aim to suggest the real risk of alcohol for developing or preventing AD.

Contents

1. Introduction

Alzheimer's disease (AD), the most common form of dementia affecting populations aged over 65 years worldwide, is sporadic, genetically non-obvious, and rarely inherited (1). The main well-known pathological features of the disease include the abnormal extracellular deposition of misfolded amyloid-β (Aβ) senile plaques in brain parenchyma and cerebral vessels, the intracellular accumulation of hyperphosphorylated tau (τ) in neurofibrillary tangles (NFTs), chronic neuroinflammation, neuronal loss and severe brain atrophy as well as progressive loss of memory (2,3). Consequently, in the last 30 years, the deregulation of Aβ metabolism (oligomerization, aggregation and plaque formation) has been the major target for therapeutic intervention (4), and only marginal effects have been registered (5-7), suggesting the need for preventive/curative treatments or alternative solutions.

Therefore, although the causes of AD remain unknown and cures or universally effective treatments, are not available, most experts have highlighted a broad constellation of contributing risk factors. Among these risk factors, alcohol consumption, associated with extensive cognitive problems (8), including alcoholic dementia (9), has been targeted. Similar features have been denoted between the effects of alcohol on cognition, brain disorder and brain biochemistry with the biological effects of AD, suggesting that the use of alcohol may constitute a risk for aggravating or developing AD (10). In line with this view, AD patients with a habitual drinking history have shown cognitive improvement during the clinical course of abstinence (11). By contrast, this effect was not observed in patients consuming high amounts of alcohol prior to diagnosis of AD (11). In line with these data, there is another emerging body of literature that contends alcohol consumption, particularly red wine, may rather serve as a protective factor for cognitive decline (12,13). Several epidemiological studies have shown that low or moderate wine consumption can be effective in retarding age-related cognitive decline (14), possibly linked to polyphenols present in beverages.

However, the studies promoting the benefits of alcohol on AD exclusively focus on moderate alcohol consumption (12), the restriction of alcohol to only an elderly population (13), and broad classification of cognitive decline (15). Relevant issues remained regarding the protection, the aggravating or detrimental effects of alcohol consumption or whether protective effects are simply influenced by the quantity and/or frequency of drinking. Despite the limiting factors identified regarding the beneficial effects of alcohol consumption (16), a single-target therapeutic strategy appears to produce only suboptimal results and a broader neuroprotective approach, at least theoretically, appears more appealing (17). Thus, the aim of the present review was to discuss the association between alcohol consumption and AD.

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2. Alcohol consumption as a risk factor for developing AD

Heavy alcohol consumption impairs cognitive performance with immediate and long-term effects on the brain anatomy and neuropsychological functioning (18-21). Cognitive impairment is related to clinical dementia as it accelerates shrinkage and atrophy of the brain, leading to critical determinant of neurodegenerative changes and cognitive decline in aging (22). However, these morphological changes induced by alcohol consumption may be reversible unlike AD or aging (23), as atrophy decreases, with cognitive improvement after abstinence from alcohol (24,25). Other data showed that morphological changes in the brain are associated with the loss of a number of nerve cells occurring in the white matter, which largely comprises nerve fibers that connect neurons (26) and/or cortical cholinergic neurons (24), known to be affected in AD. This link renders plausible that alcohol use may be linked to AD as the cholinergic system plays an important role in memory. This role is confirmed and its deficits are well established in AD (27). Chronic alcohol use causes degeneration of cholinergic neurons (28), or decreases receptors of cholinergic system in AD. These may aggravate the reduction of cholinergic neurons already present in AD patients. However, the improvement of cognitive function in alcoholics after abstention from alcohol suggests that cognitive deficits may reflect neurochemical alterations rather than neuronal loss (24,28). Therefore, without appearing as an accelerator of AD process, alcohol may induce its effects on the cholinergic system, independently from the cholinergic deficits caused by AD (29,30). However, alcohol-related brain damage appears to differ in young and older alcohol consumers (24), although data suggest that alcohol abuse may accelerate aging-related changes in the brain at any age and that older adults may be more vulnerable to the effects of alcohol (8). Apart from cholinergic deficit, another negative effect of heavy alcohol consumption on cognitive function may be attributed to nutritional deficiency or vascular change (31,32), which consist of damage that may be relatively irreversible even after abstinence from heavy alcohol consumption (11).

Therefore, despite the above evidence showing cognitive detrimental effects of heavy alcohol consumption, to the best of our knowledge, no study has established a clear association between alcohol consumption and AD (33). More consistently, recent genetical study on a Japanese population provided evidence that the mitochondrial aldehyde dehydrogenase 2 (ALDH2*2, metabolizes acetaldehyde into acetate, protecting against oxidative stress and playing an important role in the development of AD), and two functional single-nucleotide polymorphisms (SNPs) of the dopamine-β-hydroxylase (*DBH*) gene, involved in the pathophysiology of alcoholism and whose activity is reduced in the neocortex of AD), did not modify the risk for developing AD, suggesting that the polymorphism of the *ALDH2* and *DBH* genes were not associated with AD (34). Nevertheless, future studies must be undertaken on other populations worldwide.

3. Potential benefits of alcohol on AD

Low-to-moderate alcohol intake is considered to protect against neurodegeneration pathology (13,15), dementia (35-39) and cognitive deterioration (40-43). Of the biologic mechanisms suggested to explain such potential beneficial effects on the brain, there are mainly the antioxidant properties of wine flavonoids (44), the effects against Aβ (45) and the prevention of ischemia or stroke by alcohol (46). Specifically, polyphenols, members of a large family of plant-derived compounds, are molecules containing one or more phenolic group. There are thousands of polyphenols that have been identified thus far including, bioflavonoids (anthocyanins, flavanols, favanols, favones, flavanones, isofavones and proanthocyanins), coumestans, ligans and stilbenoids (47). Polyphenolics are in general antioxidant molecules that reduce the *in vitro* process aggregation of Aβ, reducing the neuronal death of cortical neurons preventing neurodegeneration (48). The morin for example, a specific flavonoid described in red wine exhibited significant effects in preventing aggregation of Aβ (49). In agreement with these data, red wine Cabernet Sauvignon significantly reduced the number of Aβ plaque-induced neuropathology and attenuated a spatial memory decrease in an adult Tg2576 mouse model of AD (50). Another flavonoid that plays an important role in red wine is resveratrol. Resveratrol is known to protect against cardiovascular diseases (which are risk factors for developing AD) and various types of cancer, together with the promotion of the antiaging effect, the modulation of pathomechanisms of debilitating neurological disorder such as strokes, ischemia and Huntington's disease, as well as protection against neuronal degeneration (14,51). Other natural molecules including fulvic acid, altered the aggregation mechanism of τ proteins, a critical protein involved in the stabilization of microtubule and axonal transport, found to be involved in AD pathogenesis (52). However, whatever the facts around the benefits that may follow the potential benefits of low-to-moderate consumption of alcohol, the importance of drinking patterns and specific beverages consumed remain elusive. The operational definition of low or moderate drinking which may vary greatly across studies (53) and the concept of a moderate drinker, which may also be imprecise, comprising a wide range measure that may include those consuming less than one drink a day (54). Red wine consumption appears to promote far more protective effects than the consumption of other ethanol containing beverages (55). This is in keeping with variations that may be introduced by consumers who sometimes associate the consumption of tobacco, or the possible toxicity effects of chronic exposure of the liver to alcohol (56), which can also contribute to brain alteration in regions involved in memory (57).

Taken together, the data provide insufficient evidence to suggest abstainers should initiate alcohol consumption to protect against dementia or AD.

4. Conclusion

Based on the abovementioned research data, no relationship between alcohol consumption and AD exists. In addition, although low-to-moderate consumption of alcohol may protect against AD, leading to benefits on neurodegeneration, Aβ, oxidative stress and τ neurofibrilary tangle formation suggest bias regarding the definition of low-to-moderate consumption as well as the variability of beverages containing alcohol. In addition, the absence of studies on the possible side effects of

chronic exposure to alcohol on peripheral organs such as liver, and kidney lead to the necessity to delineate global and standard protocols for advanced studies. These studies render the benefits associated with low-to-moderate alcohol consumption against AD. However, the results should be considered as controversial and insufficient to suggest abstainers that initiate alcohol consumption in a preventive manner against AD.

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