ISSN NO. 2320-5407

Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/18445
DOI URL: http://dx.doi.org/10.21474/IJAR01/18445

RESEARCH ARTICLE

EFFECT OF ALCOHOL ON LEWY BODY DEMENTIA

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Manuscript Info

Manuscript History
Received: 18 January 2024
Final Accepted: 21 February 2024
Published: March 2024

Abstract

Lewy Body Dementia (LBD) is a neurodegenerative disorder with complex pathological mechanisms. These contribute to neurodegeneration, affecting cognitive and motor functions. LBD holds substantial prevalence, impacting both cognitive and motor domains. Understanding the potential influence of alcohol on LBD is pivotal due to its widespread societal consumption. The aggregation of alpha-synuclein contributes to neuronal dysfunction and degeneration. Dopaminergic dysfunction is a hallmark of LBD, influencing motor symptoms and contributing to cognitive decline. Disruptions in dopaminergic pathways significantly impact disease progression. Alcohol exhibits a potential to interact with alpha-synuclein, influencing its aggregation and contributing to the neuropathological processes observed in LBD. Alcohol's impact extends to neurotransmitter modulation and synaptic dysfunction. Disruptions in these crucial processes may exacerbate the neurodegenerative cascade seen in LBD. Contrastingly, specific components within alcoholic beverages may possess neuroprotective properties, potentially mitigating aspects of LBD pathology. Future directions include the development of the criteria for early diagnosis (prodromal DLB) and the establishment of new biomarkers that directly indicate Lewy-related pathology, including α-synuclein imaging, biopsies of peripheral tissues (skin, etc.) for the demonstration of α-synuclein deposition, and biochemical markers (cerebrospinal fluid/blood), as well as the pathological evaluation of the sensitivity and specificity of the 2017 revised diagnostic criteria.

Lewy Body Dementia (LBD) is a neurodegenerative disorder with complex pathological mechanisms. This scientific review explores the relationship between alcohol consumption and LBD. LBD is characterized by the accumulation of Lewy bodies, and intracellular fibrils containing alpha-synuclein.

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Introduction:-

Lewy Body Dementia (LBD) is a complex and challenging neurodegenerative disorder characterised by the presence of Lewy bodies and alpha-synuclein aggregation in the brain. It has gained recognition due to its significant impact on cognitive and motor functions, often blurring the lines between Parkinson's disease and Alzheimer's disease. Researching potential factors contributing to LBD is crucial for understanding its aetiology and developing effective treatments. Among these factors, the role of alcohol in the development and progression of LBD is an area of interest. As a widespread substance, alcohol's impact on neurological health, particularly concerning Lewy Body Dementia, necessitates comprehensive understanding. This paper deals with the neurobiological basis of LBD, explores potential mechanisms underlying alcohol-related effects on Lewy body pathology, and discusses the possibility of alcohol's protective effects against LBD. Through an examination of existing literature, this paper aims to contribute to the evolving understanding of the link between alcohol consumption and Lewy Body Dementia, offering insights that may inform future research.

Background of Lewy Body Dementia (LBD)

Lewy Body Dementia is a disease identified by abnormal deposits of the protein alpha-synuclein in the brain. These deposits are called Lewy Bodies and affect areas in the brain associated with cognition, motor control and memory. Its symptoms include- Movement disorders, Visual Hallucinations, Cognitive problems, and Sleep disorders among others. It is a progressive disease, which means that the symptoms get worse with time. There is no cure for this disease but many of the symptoms can be temporarily relieved with medication such as Cholinesterase inhibitors which help manage cognitive symptoms, and Levodopa to treat motion-related symptoms.

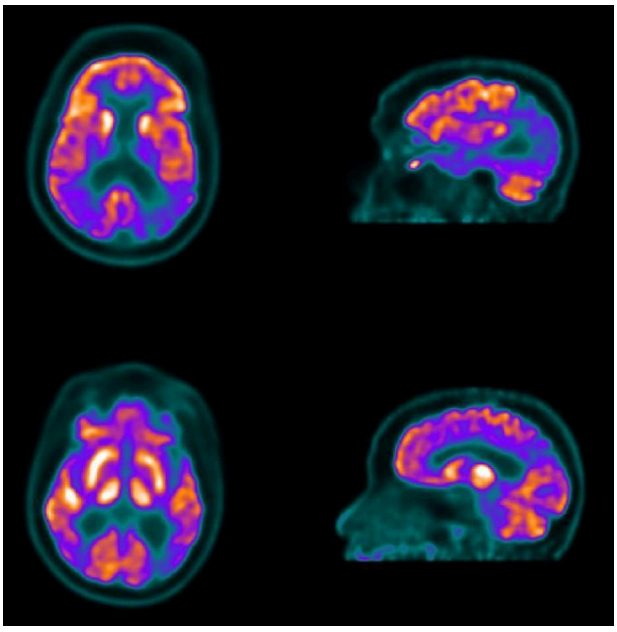

Fig. 1:- Shows an example of PET findings in Lewy Body Dementia. Note marked hypometabolism in parietal and occipital regions of the brain, a distinct pattern from Alzheimer's Disease.

Prevalence of LBD

According to a clinical study conducted in the UK, Patients with DLB(Dementia with Lewy bodies) comprised 4.6% of all dementia cases and the frequency of clinical diagnosis of DLB varied between geographical regions in the UK, and the prevalence of DLB was much lower than expected in this case series, which suggests considerable under-diagnosis of the disorder. In the general population, Prevalence estimates of DLB range from 0% to 5% and from 0% to 30.5% of all dementia cases.

Neurobiological Basis of Lewy Body Dementia

Lewy Bodies and Alpha-Synuclein Aggregation

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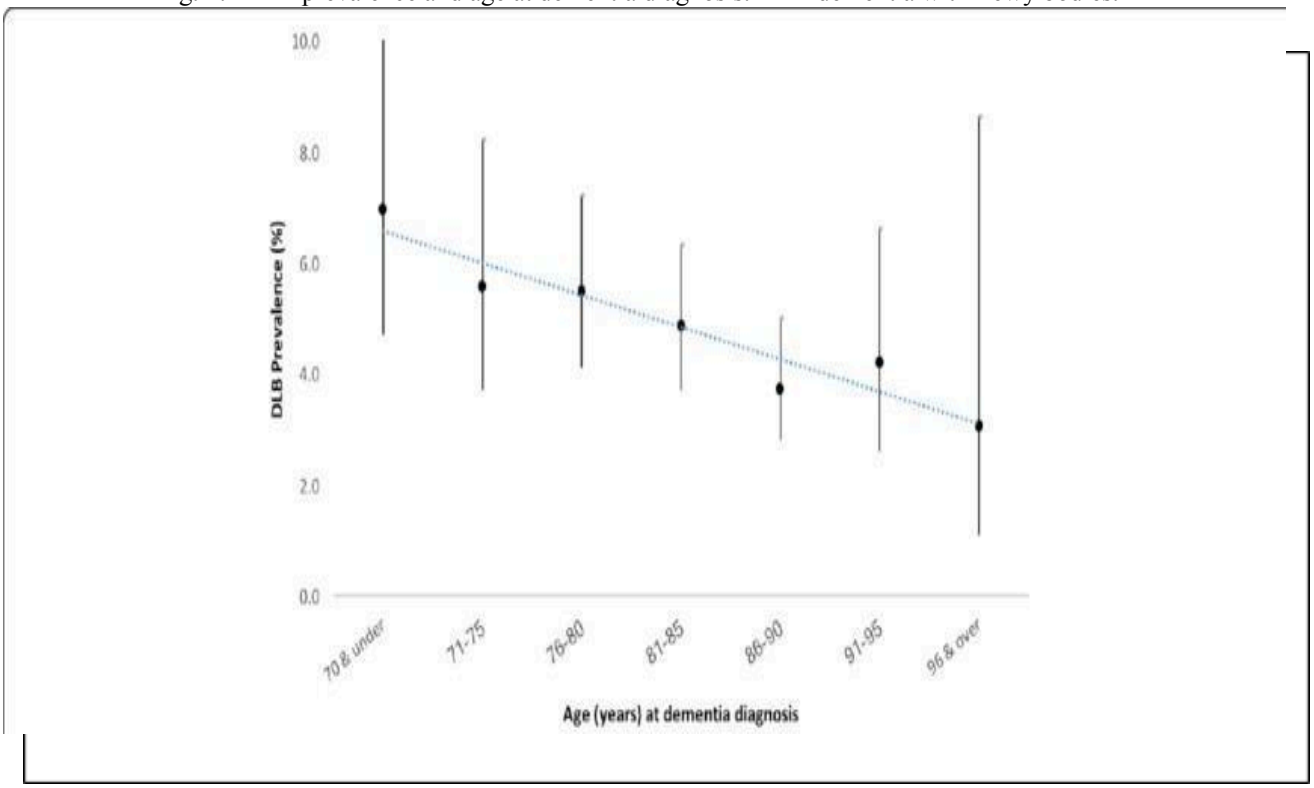
Alpha-synuclein is a 140 amino acid, natively unfolded protein predominantly localised in the presynaptic terminals of neurons, It is a cytoplasmic proteinaceous and lipid-rich inclusion that represents a key pathological hallmark of Parkinson's disease(PD)and other neurodegenerative diseases, collectively referred to as synucleinopathies. Several lines of evidence from neuropathological studies, human genetics, and cellular and animal models support the hypothesis that aSyn plays a central role in the formation of Lewy pathologies. Under normal conditions, α-synuclein exists as a randomly structured and natively unfolded protein and remains as a monomer within the cytoplasm. Under pathological conditions, α-synuclein undergoes conformational changes which cause the monomers to aggregate with each other and become insoluble, adopting a β-sheet-rich structure. This facilitates its aggregation into oligomers, protofibrils, and insoluble fibrils that accumulate in Lewy bodies

Fig. 2:- DLB prevalence and age at dementia diagnosis. DLB dementia with Lewy bodies.



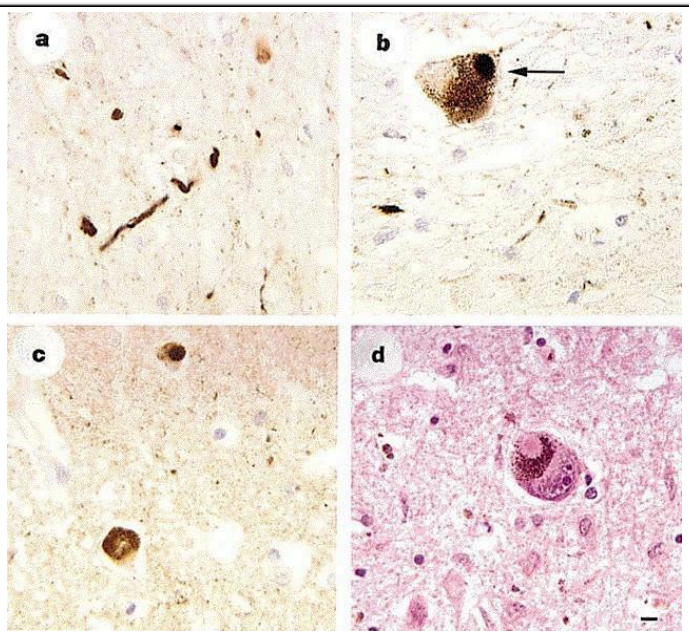


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Figure 3:- Tissue from patients with DLB (from the tissue collection of the Department of Pathology and Laboratory Medicine, University of Pennsylvania) immunostained for α-synuclein.

The accumulation of aSyn and its propensity to form fibrils is a key requirement for the formation of Lewy Bodies. Recent studies have shown that LBs are highly enriched with β-sheet structures and also contain cross-β-sheet structures, both of which are key features of all amyloid fibrils and recombinant aSyn fibrils produced in vitro.

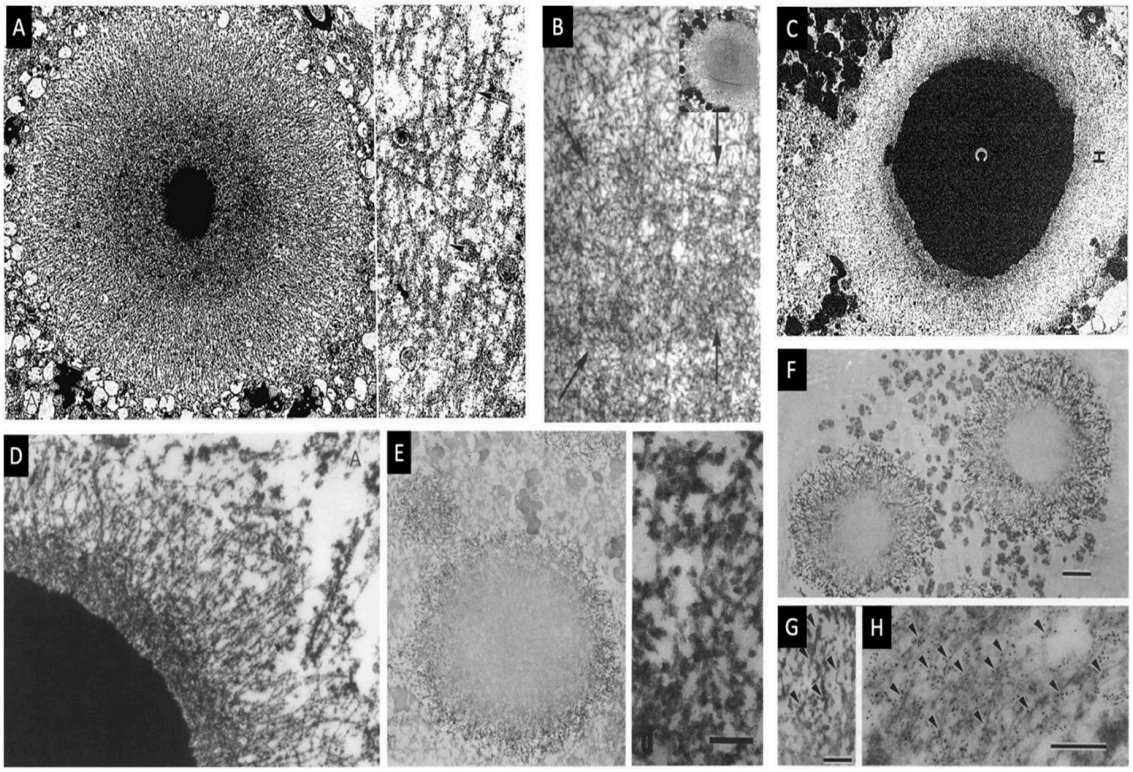

Fig.4:-Ultrastructure of LBs: A collection of images of LBs from different studies revealing their common features of a dense core and radiating filaments, the images show that LB structuresare rich in filamentous structures.

Dopaminergic Dysfunction in LBD

Depression is commonly observed in Lewy body disorders (LBD) and is associated with cognitive impairment and a faster rate of cognitive decline, given the role of dopamine in the development of movement disorders, but also in motivation and reward. LBD cases with depression showed significantly higher α‑syn levels in SN, VTA and NAcc, suggesting that the levels of α‑syn pathology may be one of the main factors driving this.
Alpha‑synuclein interaction with dopamine metabolism and transmission may have important implications not only in neuronal loss and motor symptoms but also through the development of depressive symptoms in LBD. The conclusions reached suggest that dopaminergic α‑synuclein pathology appears to drive depression. Targeting
dopaminergic pathways may also provide symptomatic relief for depressive symptoms in LBD patients.

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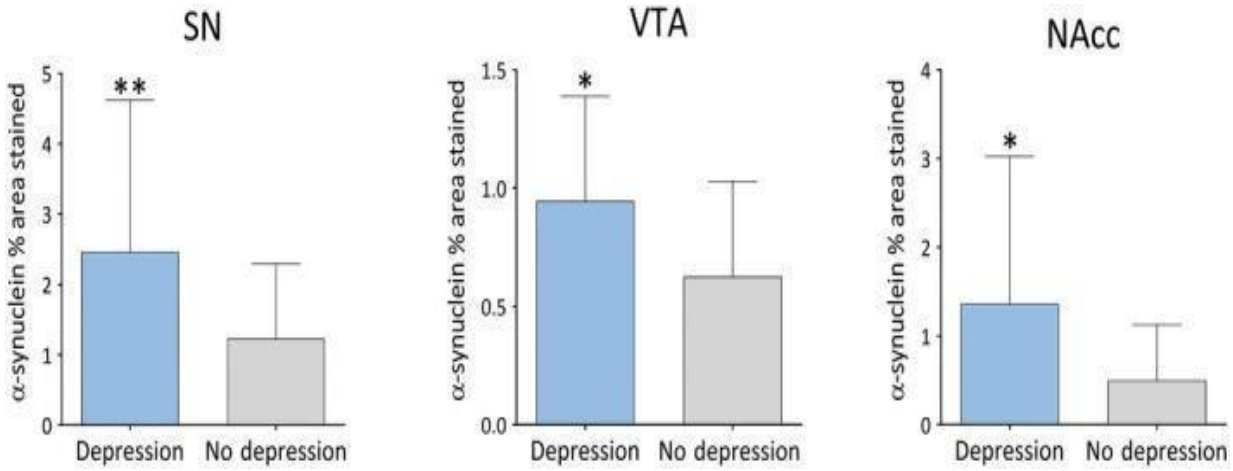

Fig. 5:-α‑synuclein burden in depressed vs. non‑depressed LBD cases.Significant pathological changes (% area stained) in depressed vs. nondepressed LBD cases. Significance levels set at *P < 0.05, **P < 0.01 and ***P < 0.00

Mechanisms of Alcohol-Related Effects on Lewy BodyPathology

Interaction of Alcohol with Alpha-Synuclein

Genome-wide association studies (GWAS) have found α-Syn to be the topmost candidate gene for alcoholism. Alcohol modulates α-Syn protein expression, and this may be via an iron-dependent mechanism. Increases in iron in the brains of alcoholics are likely to lead to differences in the expression and aggregation of α-Syn. At the epidemiological level, a history of AUD was shown to confer an increased risk ofPD(Parkinson's Disease) symptoms in both men and women with a higher risk at lower ages with PD. Although low-to-moderate beer consumption had a lower PD risk, greater liquor consumption with higher alcohol content had a higher PD risk, while wine consumption did not have any associated risk of PD. Pure alcohol induces oxidative stress acts as a pro-oxidant and may also be pro-inflammatory. Substantial damage to the substantia nigra, an area of the brain associated with PD, has been observed in chronic alcoholics

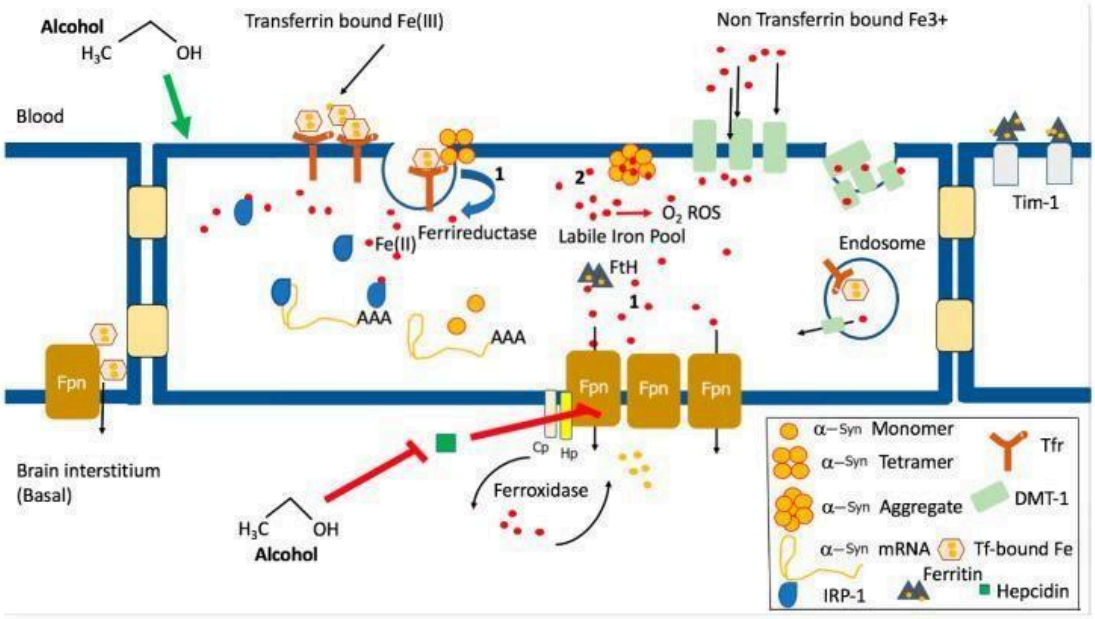

Fig. 6:- Uptake and export of iron from endothelial cells of the blood–brain barrier are likely increased in alcohol use disorder, leading to brain iron dyshomeostasis. Alcohol misuse leads to systemic iron overload and increased expression of α-synuclein.

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Synaptic Dysfunction

Ethanol(EtOH) has effects on numerous cellular molecular targets, and alterations in synaptic function are prominent among these effects. Acute exposure to EtOH activates or inhibits the function of proteins involved in synaptic transmission, while chronic exposure often produces opposing and/or compensatory/homeostatic effects on the expression, localization, and function of these proteins. The most commonly studied forms of long-lasting synaptic plasticity are long-term potentiation (LTP), a persistent increase in synaptic transmission, and long-term depression (LTD), a persistent decrease in transmission. Acute EtOH exposure generally suppresses the induction of LTP at this and other synapses. Effects occur at EtOH concentrations associated with intoxication and in some studies at surprisingly low concentrations.

Neuroprotective Properties of Certain Alcoholic Compounds

1. A case-control study by Bachmann and colleagues analysed three assumed major risk factors (head trauma, smoking, and alcohol consumption) for dementia in African and European American individuals with dementia and their non-affected siblings. Alcohol consumption over an average of 0.25 US standard drinks per day was associated with lower dementia risk in both groups.

2. In the Rotterdam Study, a large cohort study in elderly patients (over 55 years old), moderate drinking was defined as 1–3 drinks per day and resulted in a significant risk reduction for any form of dementia

3. The Whitehall-II-Study confirmed these findings in a younger population of civil service employees aged 35–55 years at study inclusion (9087 participants of which 397 developed dementia). Similar to the Rotterdam Study, the risk for developing dementia was lowest in the individuals consuming between 1 and 14 drinks per week

4.The HUNT study from Norway, encompassing almost the whole population of a community in Northern Norway(40,435 participants) showed no association of dementia with low or moderate alcohol consumption.

Low to average alcohol consumption does not increase the risk of dementia significantly, it might be even protective. High-level alcohol consumption (>14 drink units/week) is linked to an increase in dementia risk.

Conclusion:-

In conclusion, this paper gives a nuanced understanding of the neurobiological basis of LBD, characterised by Lewy bodies and alpha-synuclein aggregation, along with dopaminergic dysfunction, providing a foundational understanding of the pathology. Examining the mechanisms through which alcohol influences Lewy Body pathology, particularly its interaction with alpha-synuclein and induction of synaptic dysfunction, provides a link between alcohol consumption and the neurodegenerative processes associated with LBD. The exploration of the potential protective effects of alcohol, emphasises the neuroprotective properties inherent in certain alcoholic compounds. The significance of this review extends beyond the scientific community, as it holds implications for public health and the development of strategies aimed at minimising the impact of Lewy Body Dementia on individuals and society at large.

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