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REVIEW ARTICLE **OPEN ACCESS**

Alcoholism: A Cascade of Cellular Insult to Cerebellum & Mitochondria

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ABSTRACT
Alcoholism is a module which combines the existing fields of cerebellar degeneration and mitochondrial myopathy under one umbrella. Alcohol is a depressant drug for the brain and its excessive consumption is associated with damage of various body tissues. Therefore alcoholism is a large public health concern throughout the world. Excessive long term use of alcohol cause the sudden movement disorders like inability in motor coordination and mitochondrial myopathy due to its damaging effects on cerebellum part of the brain. The cerebellar dysfunction and mitochondrial impairments ultimately lead to the loss of function of voluntary muscles. The present review provides an overview of the nexus in terms of alcohol intoxication which leads to the loss of motor coordination as a result of cerebellar dysfunctions and mitochondrial myopathy.
Keywords*: Alcohol, Cerebellum Degeneration, Mitochondrial Myopathy*

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INTRODUCTION

Cerebellumis one of the prominent structures of brain that specifies the importance of a number of functions such as subtle control, motor coordination, maintaining balance and regulating muscle movement in living organisms [1]. The cerebellum is connected to the brainstem that participates in control of voluntary muscle movement, muscle tone and equilibrium [2, 3]. The cerebellum is necessary for coordination of body movements, control the stance positions and way of walking and also adjust the muscle tone of the human body [4]. Furthermore, it also initiates and controls muscle movements like position, balance and way of talking with voice as a result of balancing of smooth muscle activity [5]. The cerebellum also obtains information from the nerves by synaptic transmission which control and coordinate the muscle movements of the body. The cerebellum is also important for learning, motor behavior and control motor coordination of living organisms, thereby showing its role in higher order cognitive and poignant activity of inner feeling [6]. The damage in cerebellum can lead to the lean and weak muscles, slow speech & uncontrolled eye movement. It can also lead to shaking movement of the body parts and imbalance in the walking which leads to the sudden falling [7]. It may also affect cognitive function such as memory and emotional response while causing paralysis or intellectual impairment which might lead to imbalance, slower movements and shaking of body [8].

Alcohol has profound short and long-term impacts on the brain, particularly the cerebellum, during development and maturation [9]. Purkinje neurons also known as GABAergic neurons which are found in nuclear region of cerebellum control the relax actions of cerebellar cortex [10]. Upon ethanol sensitivity sudden action of potential dependent and independent transmission of GABAergic area with purkinje neurons by the process of presynaptic transmission have been shown to occur [11]. A presynaptic mechanism has been discovered to promote spontaneous action potential-dependent and independent GABAergic transmission in purkinje neurons [12]. Recent research has found that ethanol consumption boosts GABAergic transmission at the purkinje neuron level, which aids in the calcium release mechanism from presynaptic internal reserves [13]. The results related to GABAergic transmission are responsible for the cerebellum impairment including short term alcoholism [14].Alcohol may be a life-threatening form of acute or sub-acute myopathy to chronic myopathy [15]. The short term form of alcohol toxicity possibly results in the unswerving harmful effects of acetaldehyde, alcohol (EtOH) and also other ethanol related metabolites. An indirect development of atrophy, wasting and weakness in muscle are some characteristics of chronic syndrome related to alcoholism [16]. After the short term alcohol dinking, acute

myopathy may originate due to the high amount of binge-drinking in various days but after a long term of high alcohol drinking the person may develop the chronic alcoholic myopathy [17]. People who consume alcohol for more than 3 years as an amount between 80 to 100 gram-alcohol/day they may develop a condition of muscular wasting or atrophy [16]. Moreover, due to low protein content and low serum urea nitrogen level, intoxication of various alcoholic beverages may lead to malnutrition especially in decreasing nitrogen level. In the body of chronic alcoholic person the protein molecules are broken down, which if exceeds the ratio of synthesis of muscle proteins may lead to serious functional disturbance. ROS increased in the alcoholic person's skeletal muscles may lead to increase in the oxidative stress [18].
Because the brain is one of the body's most complex organ systems, and the cerebellum is a portion of the brain where neurons degenerate and die as a result of alcohol consumption. Long term alcohol abuse causes some deleterious effects, not only on the liver but also on the brain regions mostly on neuron cells. The cerebellum, a part of the brain important for coordinating bodily movement and possibly other types of learning behaviour, appears to be susceptible to thiamine shortage in those who have consumed alcohol. The present approach hypothesized the effects of alcohol on cerebellar degeneration and mitochondrial myopathy and therefore presents a view in understanding the mechanism of alcoholic cerebellar degeneration and muscular dysfunction in the presence of chronic/long term alcohol consumption.

TERATOGENIC EFFECTS OF ALCOHOL ON BRAIN

From youth through maturity, a considerable portion of the population consumes ethanol or alcohol. Alcoholism causes a public health hazard, as well as the threat of spreading other diseases like cardiovascular, hepatic, and mental illnesses. As a result, binge drinking and ethanol consumption have harmful consequences on the brain. Hence long term consumption of alcohol may give rise to alcoholic cerebellar degeneration (ACD) and mitochondrial myopathy (MM).

Alcoholic Cerebellar Degeneration (ACD)

The cerebellum comprises around 80% of the brain's neurons, and its degeneration affects other parts of the central nervous system, including the brain stem, cerebral cortex, and spinal cord [19]. Alcohol abuse is regarded as a leading cause of death and depression, with serious health and financial repercussions. Alcohol intoxication has a wide range of effects. One of the most common causes of cerebellar ataxia is alcohol-induced cerebellar degeneration [9]. Cerebellar degeneration is primarily characterized by slow, unsteady and jerky movement of the arms and legs, uncoordinated & jerky walk that is usually associated by agitation in the trunk of the body, slowed & slurred speech and nystagmus [20]. There are many factors that cause shrinkage of the cerebellum like hereditary degeneration or toxins like alcohol.

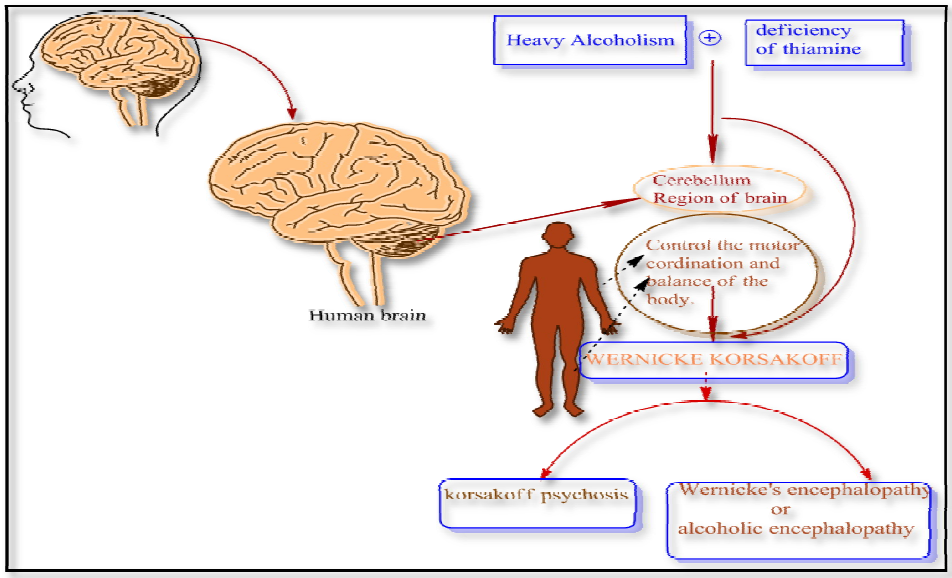

Figure 1. Effects of heavy alcoholism with thiamine deficiency on cerebellum

It is generally known that genes with a large impact on alcohol metabolism influence how people react to alcohol and how likely they are to develop an addiction to it [21]. Chronic alcoholism has many deleterious effects on the individual's brain in the form of neuropsychological abnormalities [22]. A specific range of deficits has been observed in individuals with localized damage to the cerebellum that has been termed as Cerebellar Cognitive Affective Syndrome (CCAS) [23]. Some alcohol induced disorders

like Wernicke-Korsakoff syndrome seriously affect language, mental functions and memory [24]. Chronic ethanol exposure increases protein levels of receptor subunits and cortical neurons in mouse brains, but acute ethanol exposure blocks activated ionic currents in numerous areas of the brain and the NMDA receptor-mediated extracellular calcium influx mechanism [25]. The Cerebellar Cognitive Affective Syndrome (CCAS) is defined as a deficiency of syntactical processing, spatial perception, and affect regulation in the cerebellum.It results from injury to the cerebellum's posterior lobe (lobules VI, VII, and potentially lobule IX), and is thought to represent dysmetria of thought similar to dysmetria of motor control caused by damage to the cerebellum's anterior lobe (lobules III–V) and lobule VIII [26]. Wernicke-Korsakoff syndrome is characterized by memory loss that involve loss of previously established memories or loss of the ability to learn new information due to heavy drinking [27].The prime etiology of Wernicke-Korsakoff syndrome is thiamine deficiency (Figure 1). Several key enzymes maintain the homeostasis of cerebrum by the help of thiamine as cofactor. The important enzymes are pyruvate dehydrogenase, α-keto glutarate dehydrogenase of the TCA cycle and transketolase of the pentose-phosphate pathway [28].

Toxic intermediates build due to a decrease in enzyme activity and lactic acid generation is increased when pyruvate is converted to acetyl coenzyme A due to thiamine shortage. Tissue injury occurs when toxic intermediates build up in areas of the brain with high metabolic demand and thiamine turnover, limiting metabolism [29]. Some physical and mental abnormalities include joint and cardiac deficits, delay in motor & balance control of body and reflex development and ultimately death of neurons in the cerebellum due to deleterious effect of alcohol [30].

In the brain, heart, and skeletal muscles, ethanol metabolism is mostly linked to the production of both ROS and RNS, which create a favourable environment for oxidative stress formation in the cells and also induce oxidative degradation of the mitochondrial genome (Figure 2). These ethanol-induced effects could play a role in the development of mitochondrial encephalomyopathy and brain damage. Alcohol is one of the most often abused narcotics on the planet. Long lasting consumption of alcohol can shrink the frontal lobes of the brain that cause impairment in thinking skills [31]. According to a report by the World Health Organization, more than 11% of Indians binge drink, compared to a global average of 16% [32]. Chronic ethanol exposure destroys neuron cells, reduces neuron survival, and causes a variety of brain developmental abnormalities [31]. Acute ingestion of alcoholic beverages at low concentrations promotes euphoria, relaxation, and reduces stress or anxiety, while a concentration (10-50mM) has a selective and specific action on certain proteins at the physiological level [33].

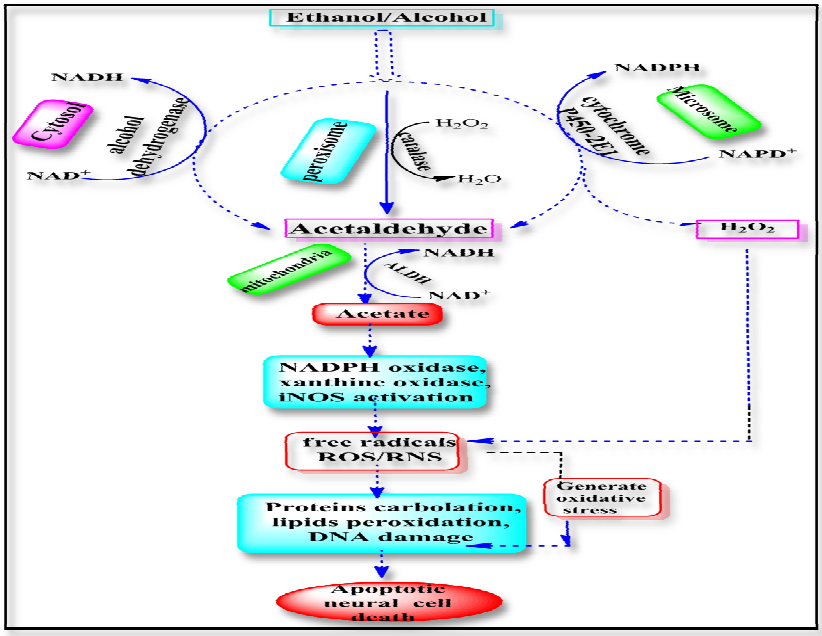

Figure 2. Oxidative pathway of alcohol metabolism and interaction of different enzymes during alcohol metabolism. The enzymes alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1) and catalase all contribute to oxidative metabolism of alcohol.

Mitochondrial Myopathy (MM)

Mitochondria are vital cellular organelles that produce ATP and play a role in anti-oxidant defence, fatty acid oxidation, intermediate metabolism and cell death. Mitochondria are an inexplicable source of energy that govern a variety of metabolic activities and are constantly fissioning and fusing throughout cell growth [34]. Mitochondria are responsible for producing most of the energy which is needed for our cells to function (Figure 3) [35].

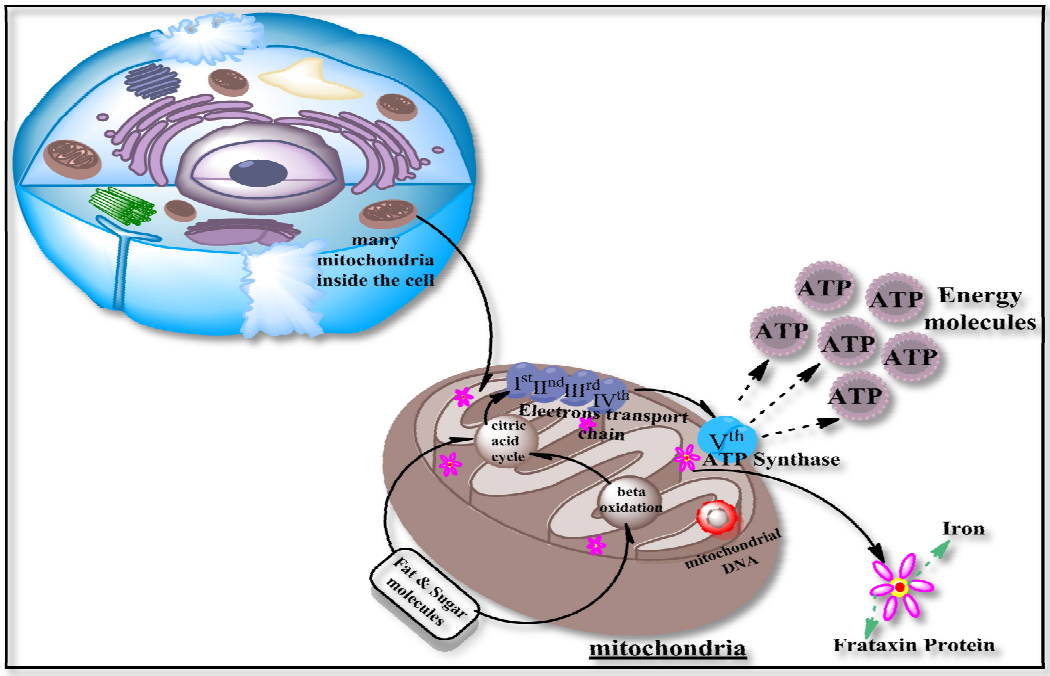

Figure 3. Mechanism of energy formation in mitochondria of the cells. Electrons are passed through the major complex (complexes I, II,III, IV and V) of the electron transport chain (Complexes I through IV shuttle the electrons down the line) and complex V actually churns out ATP, so it's also called ATP synthase, ATP is made by ATP synthase.

The condition of perplexed muscular movement is regarded as myopathy in which muscle fibers tend to obstruct their functions (Table 1). Myopathy is a mitochondrial disease that causes obvious muscular issues (myo refers to muscle, and pathos refers to disease), while mitochondrial encephalomyopathy is a condition that encompasses both muscular and neurological disorders (encephalo means the brain, myo means muscle, and pathos means disease) [36]. Chronic intoxication with ethanol produces oxidative damage to mitochondrial proteins, phospholipids, and DNA in the liver, brain, heart, and skeletal muscles [37].

TABLE 1. Different kinds of myopathies, their onset period and antagonistic approach towards muscles

Different kinds of Myopathy	Onset period	Clinical finding	References
Congenital myopathy	Appear at birth or in infancy	Hypotonia, Hyporeflexia, Nocturnal hypoventilation	[44]
Distal myopathy	Appear from child to adulthood	Dysphasia, Dysphonia & weakness in upper & lower limbs	[45]
Endocrine myopathy	Appear in adulthood	Hypothyroidism, Hyperthyroidism Hyperparathyroidism, Hypoparathyroidism	[46]
Inflammatory myopathy	Appear both in children, adult & old age group	wasting & weakness of proximal muscles and quadriceps	[47]
Metabolic myopathy	Appear in all age group	Intorelance, cramps, progressive muscle weakness	[48]
Myo-fibrillar myopathy	Appear after 40 years of age	Slow & progressive weakness in both proximal (25%) and distal muscles (80%)	[49]

Mitochondrial myopathy affects nerve and muscle cells because they require a lot of energy in the body. Atrophy or shrinkage of the muscles of the face and neck, as well as weakening and atrophy of the

muscles of the face and neck, can cause slurred speech and swallowing difficulties [38]. Low energy generation, free radical production, and high lactic acid formation in various organs of the body may be the cause of the disastrous effects caused by alcohol-induced mitochondrial myopathy [39].Chronic alcoholic myopathy (Ch-AM) develops much more gradually and lasts for longer. The main symptoms of chronic alcoholic myopathy is completely baffled muscles and atrophy in a brain which affects proximal muscles and type-2 muscle fibers [40]. The chronic type of alcoholic myopathy is characterised by gradual muscle wasting and weakening, notably in the legs [41]. Heavy drinkers have a lower lactic acid response to ischemia forearm [42]. Chronic alcohol consumption is thought to cause a change in the lactate dehydrogenase isoenzyme pattern or a decrease in lactate dehydrogenase activity [43].

EPIDEMIOLOGICAL AVENUES OF ALCOHOL ABUSE: PSYCHOLOGICAL AND SOCIETAL EFFECTS

Treatment of alcoholism is a complicated and difficult task both for the person involved and sometimes clinicians. Because alcoholism is linked to the brain and behaviour, the physician must choose a treatment strategy that may include a number of therapeutic methods to help the patient quit drinking and regain lost function. Psychological effects of alcohol may include hallucination, severe depression, nervousness, aggression and unexplained mood swing. These effects also include isolation and separation from their family, loved ones and friends. Alcoholic persons usually share their feelings with the same addicted persons and tend to remain socialize with individuals sharing a similar addiction. Therefore alcoholism is generally coupled with negative psychological and social outcomes, in addition to physical and physiological effects. Controlled drinking may be an important parameter but those patients who have reached the climax of harmfulness due to alcoholism, at least a period of abstinence is highly recommended. Need of the hour is to recognise the patients who are experiencing difficulties with alcohol and sympathetically help them to move forward. Although mild consumption of alcohol results in beneficial effects but long term use of alcohol has severe negative life-threatening effects on multiple organs [50]. PET (positron emission tomography) is a technique of neuroimaging that allows the clinician to visualize and quantify in the patient the effects of alcohol on brain and other chronic disease on different neurotransmitter systems. Refraining from alcohol results in the regeneration of neurons to some extent which is the mainstay of management towards alcoholism [51, 52].

CONCLUSIONS

As we all know, alcohol can cause measurable memory deficits after only a few drinks, and as the amount of alcohol consumed grows, so does the degree of impairment. When a big amount of alcohol is consumed, it causes a blackout and increases the risk of catastrophic brain abnormalities. Damage can occur either directly from alcohol's effects on the brain or indirectly through liver illness and other conditions. The cerebellum, a part of the brain that coordinates body movement and possibly other types of learning processes, appears to be vulnerable to the effects of thiamine shortage in those who have consumed alcohol. The present approach hypothesized the effects of alcohol on cerebellar degeneration and mitochondrial myopathy, therefore, presents an overview in understanding the mechanism of alcoholic cerebellar degeneration and muscular dysfunction in the presence of chronic/long term alcohol consumption.

ABBREVIATIONS

EtOH, ethanol; WKS, Wernicke Korsakoff; CCAS, Cerebellar Cognitive Affective Syndrome; ACD, Alcohol cerebellar degeneration; MM, Mitochondrial myopathy; WHO, World Health Organization; Ch-AM, Chronic alcoholic myopathy; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; CNS, Central nervous system; PET Positron Emission Tomography; ADH, Alcohol dehydrogenase; CYP2E1, cytochrome P450 2E1.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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