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ETHANOL AND POLYNEUROPATHY

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Abstract: The primary aim of this systematic review was to establish the prevalence, character, and risk factors of peripheral neuropathy amongst chronic alcohol abusers and to identify the most appropriate management strategies. In this review, possible pathogenetic mechanisms are also discussed. A systematic, computer-based search was conducted using the PubMed database. Data regarding the above parameters were extracted. 87 articles were included in this review, 29 case–control studies, 52 prospective/retrospective cohort studies and 2 randomised control trials, 1 cross sectional study, and 3 population-based studies. The prevalence of peripheral neuropathy amongst chronic alcohol abusers is 46.3% (CI 35.7– 57.3%) when confirmed via nerve conduction studies. Alcohol-related peripheral neuropathy generally presents as a progressive, predominantly sensory axonal length-dependent neuropathy. The most important risk factor for alcohol-related peripheral neuropathy is the total lifetime dose of ethanol, although other risk factors have been identified including genetic, male gender, and type of alcohol consumed. At present, it is unclear what the pathogenetic mechanisms for the development of neuropathy amongst those who chronically abuse alcohol are, and therefore, it is unknown whether it is attributed to the direct toxic effects of ethanol or another currently unidentified factor. There is presently sparse data to support a particular management strategy in alcohol-related peripheral neuropathy, but the limited data available appears to support the use of vitamin supplementation, particularly of B-vitamin regimens inclusive of thiamine.

Keywords: Alcohol, Alcoholic, Neuropathy, Ethanol, Polyneuropathy.

Alcohol abuse is known to cause a range of neurological disorders, including cerebellar ataxia, confusion, cognitive impairment, and peripheral neuropathy [1]. Neuropathy associated with chronic alcohol abuse may involve large and/or small (including autonomic) fibres and is rather heterogeneous in its clinicopathological features [2, 3]. The earliest known description of neuropathic symptoms associated with ingestion of alcohol were noted by Lettsom in 1787, describing the presentation of paralysis and hypoesthesia which was of greater prominence in the legs than the arms [4]. Presently, peripheral neuropathy amongst chronic alcohol abusers remains an entity of disputed character and pathogenesis. Its current obscurity is likely attributable to the complex range of physiological derangements that come with chronic alcohol abuse—many of which have the capacity to cause neuropathy. Some of the factors discussed in literature which can attribute to the neuropathy presenting in these patients are the direct toxicity of alcohol, nutritional deficiencies (particularly thiamine and B12), hepatic cirrhosis, impurities of alcoholic beverages (for instance, lead) and deranged blood glucose [3, 5, 6]. The interaction of these factors has not only complicated discerning the most important pathological mechanisms of neuropathy in alcohol abuse, but also prevented characterisation of the typical features as the various elements affect the nervous system differently. Although alcoholic toxicity is not firmly established as the only pathogenic factor in neuropathy amongst alcohol abusers, in this review the entity shall be referred to as “alcohol-related neuropathy”.

The aim of this systematic review is to characterise the presentation of alcohol-related peripheral neuropathy, to determine the typical ancillary test results, to establish the importance of various risk

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factors and to explore the likely pathogenetic mechanisms. Due to the breadth of the literature surrounding this topic, this review shall focus exclusively upon peripheral neuropathy, without discussing autonomic neuropathy.

Nine studies reported EMG findings in alcohol-related peripheral neuropathy patients. Reduced recruitment pattern of motor units was a frequently reported outcome [8]. Active denervation (presence of positive waves and fibrillations) was also present in the majority of patients. The prevalence of denervation findings on EMG ranged from muscle to muscle, with the highest being in the muscles of the lower limbs suggesting a length-dependent pattern [5]. However, one study reported normal EMG findings, which may reflect the early stages of the neuropathy in which predominantly the sensory NCS are abnormal [7] Some studies performed single-fibre EMG which reported increased fibre density in alcoholic patients, suggesting higher re-innervation rates in such patients .

Alcohol intake

Unsurprisingly, intake of alcohol has been positively correlated with prevalence of neuropathy by several authors. Wetterling et al. investigated the prevalence of peripheral neuropathy amongst chronic alcoholics ($n = 242$), splitting the cohort by drinking pattern into episodic drinkers [less frequent, irregular alcohol consumption with longer (> 5 days) sober periods, and some binges (less than one/week)], frequent heavy drinkers [frequent alcohol consumption (more than 3 days/week)] with frequent intoxication (more than one/week) and continuous drinkers (almost daily alcohol consumption without bingeing) .This study demonstrated higher rates of peripheral neuropathy amongst continuous and frequent heavy drinkers (29.6 and 29.9% respectively) than episodic drinkers (11.3%). Similarly, a study by Vittadini et al. ($n = 296$) found duration of alcohol abuse to be amongst the most important risk factors for peripheral neuropathy showing that subjective symptoms developed after a relatively short duration of abuse (1–5 years) but severe polyneuropathy after > 10 years of alcohol abuse. Ammendola et al. compared alcoholics with and without neuropathy to identify risk factors this study showed an increased duration of alcoholism amongst those with neuropathy as well as a higher total lifetime dose of ethanol (TLDE) ($n = 76$) [6]. It also identified an inverse relationship between TLDE and duration of alcoholism and sural nerve SEP amplitude. TLDE was a common factor identified in six further studies which found it to be correlated with an increasing frequency of neuropathy [10]. A study conducted by Angelink et al. also reported a correlation between neuropathy and duration of alcohol abuse; as well as neuropathy and increasing age ($n = 35$) , and one study conducted by Pessione et al. found that severity of alcoholism, TLDE and presence of other alcohol-related diseases were significantly related to the presence of neuropathy ($n = 90$) [10]. Conflicting these, two studies were unable to find a relationship between TLDE and neuropathy, though they had reasonably small populations ($n = 17$ and $n = 46$)

Sex

Some authors have identified significant relationships between sex and risk of alcohol-related neuropathy. Several studies, including a larger study by Vittadini et al., have found that there is an increased prevalence amongst males [5, 6,]. Behse and colleagues, however, found that females were more vulnerable to severe neuropathy, whilst males were overrepresented amongst mild cases, though this is based on a small study ($n = 37$). These studies did not adjust for alcohol consumption, and therefore, this may be because male subjects consume more alcohol as opposed to any biological vulnerability to alcoholic neuropathy in the male sex.

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Genetics

Rosler et al. investigated the association between HLA distribution and the physical consequences of alcoholism, including polyneuropathy, and showed that there was no relationship between alcohol-related neuropathy and a particular HLA type ($n = 63$) Masaki and colleagues investigated the role of Glu-487→Lys mutation (single nucleotide polymorphism) of the aldehyde dehydrogenase-2 (ALDH2) in alcohol-related polyneuropathy in a cohort in Japan [12]. The *ALDH2*2* mutant allele is inactive, which causes accumulation of acetaldehyde which is thought to be toxic. This study compared 21 alcoholic patients with *ALDH2*1/2*1* to 21 alcoholic patients with *ALDH2*2/2*1*. The study identified that the sensory nerve action potential amplitudes (SNAPs) of the sural and median nerves were significantly lower in the *ALDH2*2* heterozygotes than in the *ALDH2*1* homozygotes. This, therefore, could be a significant risk factor for alcohol-related neuropathy and also demonstrates that acetaldehyde toxicity may be important in alcohol-related neuropathy. However, it is important to note that although the *ALDH*2* allele is prevalent amongst East Asians (and responsible for the well-known "Asian alcohol flushing syndrome"), it is essentially absent amongst Europeans, and therefore, this specific genetic risk factor is population-specific. Family history has been implicated as a risk factor for alcoholic neuropathy. Ammendola et al. identified a larger proportion of those who abuse alcohol with neuropathy had a family history of alcoholism than those who did not have neuropathy . Similarly, Pessione et al. found a significant relationship between parental history of alcoholism and presence of neuropathy [10]. The association between family history and neuropathy was quite striking, with four times the number of patients with neuropathy having a parental history of alcoholism, compared to those without. It is unclear whether this is a consequence of inherited or environmental risk factors, though the authors suggest that it is possible that there is an inherited genetic risk of developing neuropathy or associated environmental factors. Uniquely, Vittadini and colleagues found a relationship between the type of alcohol consumed and neuropathy. Specifically, the study demonstrated worse NCS study dysfunction amongst wine drinkers, than those who drank beer or spirits alone [11]. The authors point out that this could be an anomaly due to the wine drinkers consuming more ethanol than other alcohol abusers but offer an alternative explanation that wine may contain more toxic impurities than other beverages. This aspect was not discussed in any other studies. Malnutrition has been implicated in the pathology of alcohol-related neuropathy by several authors. The data, however, is conflicting as to the role which malnutrition plays. The majority of studies which investigate the relationship between malnutrition and neuropathy focus on thiamine deficiency as an aetiological factor, drawing upon existing knowledge of Beri Beri. For the most part, the available literature indicates that alcohol-related neuropathy may occur in the absence of nutritional deficiency, and that neither the prevalence nor the severity of alcohol-related peripheral neuropathy are correlated with nutritional status [3,5]. A smaller number of publications do attribute thiamine deficiency, but generally speaking these studies were older or of lower quality evidence [9]. An alternative explanation is that comorbid nutritional deficiency in the context of alcohol-related neuropathy may either increase the risk of neuropathy or that thiamine deficiency neuropathy is often superimposed upon neuropathy caused by the toxic effects of alcohol or its metabolites.

An interesting study by Koike et al. compared the clinical and pathological features of patients with thiamine deficient neuropathy; alcoholic neuropathy without thiamine deficiency and alcoholic neuropathy with thiamine deficiency [9]. The study showed that alcohol-related neuropathy and thiamine deficient neuropathy are clinically and pathologically distinct. The study also showed that the clinicopathological features of alcoholic neuropathy are quite uniform, but that variation occurs

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with concomitant thiamine deficiency. Specifically, alcohol-related neuropathy presented with slowly progressive, sensory-dominant symptoms whilst thiamine deficiency caused acutely progressive (< 1 month in 56%) primarily motor-dominant features with loss of ambulation, although there was more variation and presentations were inclusive of sensory-dominant cases. On sural nerve biopsy, alcoholic neuropathy showed largely small fibre loss, more frequent myelin irregularly and segmental demyelination/remyelination whilst thiamine deficiency neuropathy showed more large fibre loss and more subperineural oedema. In the patient group with both thiamine deficiency and alcohol excess, the presentations and biopsies included features from across this spectrum of clinicopathological features. The authors determine that the current confusion surrounding the role of nutrition in alcohol-related neuropathy are a consequence of undetected thiamine deficiency in some series (and therefore, variation in the features of patients) and excessive emphasis of the role of malnutrition in others. They also point out that as highly sensitive measurement of thiamine levels in the form of liquid chromatography did not become widely available until the 1980s, and therefore, some author's assessments of nutritional status may have been inadequate. An association between chronic hepatic dysfunction and neuropathy has been noted by several authors [9]. This has led some authors speculate that hepatic dysfunction, most often cirrhosis, may be important to the pathogenesis of alcoholic peripheral neuropathy. Zambellis et al. ($n = 99$) found that polyneuropathy amongst alcohol abusers was significantly correlated with liver dysfunction [5]. Vittadini et al. ($n = 296$) found a significant correlation between liver disease and the severity of polyneuropathy amongst chronic alcohol abusers [6]. Conversely, other authors have failed to find any significant relationship between hepatic dysfunction and neuropathy ($n = 383$) [12].

Two small studies compared the rates of peripheral neuropathy between those with alcoholic liver disease and those without alcoholic liver disease to establish the importance of each element. Thuluvath and Triger found that 45% of those with alcoholic liver disease and 22% with non-alcoholic liver disease had peripheral neuropathy ($n = 64$) [7]. Kharbanda et al. compared patients with alcohol-related cirrhosis to those with non-alcoholic cirrhosis ($n = 33$) finding that incidence of neuropathy was 88% in alcoholic cirrhosis compared with 56% in non-alcoholic cirrhosis [12]. This difference did not reach significance, leading the author to judge that it was the hepatic dysfunction which was most important to cause the neuropathy. However, as this study is small, it does not appear to have the strength to draw such a conclusion. These studies illustrate that hepatic dysfunction is in itself a cause of neuropathy, and that it may account for some cases of alcohol-related neuropathy.

In summary, the present study makes the following conclusions regarding alcohol-related peripheral neuropathy. Alcohol-related peripheral neuropathy is common, with signs and symptoms in 44% of chronic alcohol abusers and representing 10% of polyneuropathies. When utilising NCS to identify subclinical neuropathy amongst alcohol abusers, the rate is higher.The pooled prevalence of pain amongst alcoholic neuropathy sufferers is 42%. Although this figure should be interpreted with caution as it is based on a small number of studies, it suggests that alcohol-related neuropathy is one of the least painful neuropathies .There is a need for more careful mapping and description of the symptoms of neuropathy in research and clinical practice.

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