TOPICAL REVIEW

Pathogenesis of alcoholic neuropathy

Kucera P, Balaz M, Varsik P, Kurca E

1st Department of Neurology, University Hospital, Faculty of Medicine, Comenius University, Bratislava, Slovakia. **bll@fmed.uniba.sk**

Abstract

Chronic alcoholism is a medical, economical and social problem. Motility and mental function disorders are among the complications of chronic alcoholism and have been known for more than two centuries as "alcoholic paralysis", and are caused by alcoholic neuropathy. The pathogenesis of alcoholic neuropathy does not appear to be identical with central nervous system disorders which are caused by chronic alcoholism and it seems that it results from a failure of the protection barrier systems in the peripheral nervous system.

To the pathogenesis of alcoholic neuropathy includes: 1. direct toxic effects of alcohol on the cellular population of the central nervous system and other tissues, especially of parenchymatous organs (in particular of the liver), 2. indirect metabolic and exotoxic changes mediated by malabsorption, maldigestion and secondary caloric and energy deprivation, 3. effects of genetic factors. ***(Fig. 2, Ref. 23.)***

Key words: alcoholic neuropathy, peripheral nervous system, chronic alcoholism.

The most obvious influence of regular alcohol intake is seen in the disturbance of cortical and motility function of human body. Certain changes of psychical functions attributable to alcoholic dementia and psychosis are well-described which are often connected to alcohol paralysis based on degenerative changes of the cerebellum, basal ganglia and brainstem with clinical picture of Wernickes' encephalopathy and central pontine myelinolysis. Alcohol-induced central nervous system disorders have since the ancient times been in the spotlight of medical sciences because of disturbances of psychic and motor functions. However the peripheral nerve system disorder with apparent peripheral neuropathy accompanied by disorders of the autonomic system and posterolateral columns of spinal cord is very common.

Because alcoholic neuropathy (AN) pathogenesis still lacks a clear explanation it does not have a clear place in the classification of peripheral nervous system (PNS) disorders. Certain authors classify alcoholic neuropathy as a nutritional PNS disorder (Rowland, 1995), a toxic disorder (Adams and Victor, 1993; Victor and Ropper, 2001) or a metabolic and exotoxic neuropathy (Varsik et al, 1999).

History and present

The first surprising evidence on influence of alcohol on nervous system is from Lettsom (1780), and alcoholic paralysis was described by Jackson (1822), Hun (1855) and later by Dreschfeld (1886). Morphology and clinical symptomatology of AN was characterised in detail by Dejerine (1887). Greenfield and Carmichael (1935) described the AN connected with so called subacute degenerative changes of the spinal cord while electrophysiological aspects of this type of AN were described by Behse and Buchthal (1977). Vinken and Bruyn (1970) claimed, that the classification of PNS disorders was flowed because the etiologic and morphologic aspects of various disorders were mixed up. In the pure morphological classification of PNS disorders by Sluga (1977), the neuronal, myelin sheath, interstitial tissue and mixed disorders of peripheral nerves were considered separately for the first time.

The Executive Committee of the Research Group prepared the etiological classification of the PNS disorders with AN classified in the group of acquired exotoxic PNS disorders. It still remains unclear if the PNS disorder attributed to lack of essen-

1st Department of Neurology, University Hospital, Faculty of Medicine, Comenius University, Bratislava, and Department of Neurology, University Hospital, Martin

Address for correspondence: P. Kucera, MD, 1st Dept of Neurology, University Hospital, LFUK, Mickiewiczova 13, 813 69 Bratislava, Slovakia.

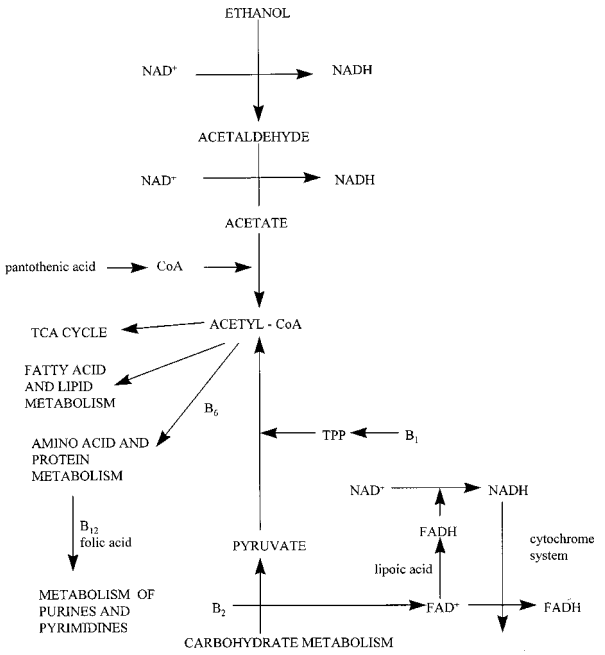

Fig. 1. Degradation of alcohol and intermediary metabolic pathways.

tial nutrients (especially thiamine) in alcoholics is present also in well nourished persons with regular intake of alcohol.

McLeod (1982) alleges doubts about the reversibility of even partial damage to PNS structures compared to the tendency of central nerve system (CNS) damage (notably mental and motor) to reverse. This experience suggests the different pathogenesis of PNS and CNS damage. From various evidence in contemporary literature it seems that CNS disorders could be attributed to the exotoxic influence of alcohol, while the damage to PNS could be caused by metabolic and nutritional deficiency factors.

Pathogenesis

The epidemiological data indicate that the chronic abuse of alcohol reaches 10 % (the percent of known alcoholics summed up with "anonymous" alcoholics) in certain regions (Adams and Victor, 1993) and that the frequency of AN (combined with parenchymatous organs diseases) may range 12--30 % (Erbsloh, 1967; Scheid, 1980).

In the era of the light microscopy the morphologic changes attributable to AN were thought to be caused by demyelinisation based on the findings of Gombault at the end of 19th century and the work of Greenfield and Carmichael (1935) and Denny-Brown (1958).

The electronic microscopy proved clearly the presence of primary axonal lesion in AN (Bichhoff, 1971; Behse and Buchthal, 1977). The primary axonal damage and secondary demyelinisation of motor and sensitive fibers (especially small diameter fibers) (Ludin and Tackmann, 1984) are considered to constitute the morphologic basis of alcoholic damage to nerve tissue at present. The demyelinisation is explained as the result of a slowing-down (deceleration) of axoplasmic flow and a degradation of the quality of biological properties of axonal enzymes and proteins. This type of degeneration — so called "dying-back" — resembles the Wallerian degeneration. Without any doubt ethanol and its toxic degradation metabolites affect neuronal metabolism including the metabolic pathways of nucleus, lysosomes, peroxisomes, endoplasmatic reticule and cytoplasm. Alcohol enters the blood as early as 5 minutes after ingestion and its resorbtion peaks after 30--90 minutes. The resorbtion is increased in the subjects with gastric disorders and in women. The alcohol gradually enters the cerebrospinal fluid, alveoli, urine and stool.

The study of Fennely et al (1967) contributed important findings of decreased levels of B1, B2, B6 a B12 vitamins, nicotinic acid, folic acid, lipoic acid, biotine and pantothenic acid to less than 50 % of usual values compared with healthy subjects. The decreased levels were later described to be present not only in subjects with AN, but also in alcoholics with no apparent AN (Stibler and Borg, 1986). Tomasulo et al (1986) described the 20 % increase of thiamine excretion in stool of alcoholic subjects. Stibler and Kjellin (1976) proved that the elevation of carbohydrate-deficient transferine (CDT) levels in alcoholics with a subsequent decrease to normal levels only after 2 to 4 weeks of alcohol withdrawal. The microchromatographic electro-focusing method proved that the CDT consists of two isoforms of serum transferine (with the absence of terminal sacharids: sialic acid, galactosis and N-acetylglucosamine).

These findings suggest the difficulty of clear differentiation of the immediate toxic influence of ethanol on nerve tissue from its metabolic effects connected with nutritional and vitamin deprivation often seen in alcoholics. This is one of the reasons which contributes to the classification of AN to the group of metabolic-toxic (exotoxic and endotoxic) neuropathies.

The key role in the degradation of ethanol is played by ethanol dehydrogenase and acetaldehyde dehydrogenase -- both two-step enzymatic systems by which the ethanol is converted to acetate which is further metabolised in human organism. Both systems require the availability of NAD^+ (nicotine amide adenine dinucleotide), which is reduced by both systems to NADH (reduced form of NAD^+). The acetaldehyde dehydrogenase is a mitochondrial enzyme that underwent a single aminoacid substitution (mutation) in about 50 % of the Asian population in a way similar to the genetic changes in sickle cell anaemia (1996). In individuals with such a mutated dehydrogenase who consume the alcoholic beverages, the acetaldehyde levels in organism reach values about 20 times higher than in individuals without the mutation.

A certain amount of acetaldehyde is not metabolised in usual pathways (Fig. 1) and binds irreversibly to proteins which results in the creation of cytotoxic proteins which adversely affect the function of nervous system cells. These abnormal proteins influence other cell populations especially the hepatocytes where the damage to hepatic mitochondria results in hepatic cirrhosis with reduction of energetic substrates in the liver. The action of these abnormal proteins is explained by the competi-

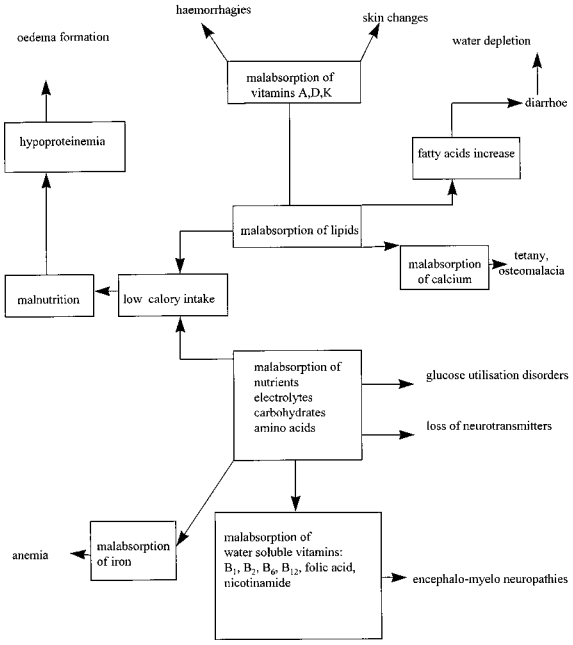

Fig. 2. Signs of malabsorption.

tion with normal proteins causing the damage to function and metabolism of the cell (Achord, 1995).

We can assume that three major systems are included the degradation of alcohol:

1) two-step dehydrogenase system as mentioned above (alcohol dehydrogenase and acetaldehyde dehydrogenase with NAD^+ coenzyme). This system is located in the cytoplasm (alcohol dehydrogenase) or mitochondrial structures (aldehyde dehydrogenase) respectively with close connections to cytochrome system,

2) peroxisomal catalase,

3) MEOS — microsomal ethanol oxidating system, located in microsomal membrane fraction, connected with the oxidation of NADPH (reduced form of nicotine amide adenine dinucleotide phosphate) to $NADP^+$ (nicotine amide adenine dinucleotide phosphate).

The toxic influence on cellular metabolism is very likely present not only in nervous cell population but also in other organs, namely the hepatocytes. The liver damage is present in about 25 % of alcoholics. It becomes congested with fat, the venules are enlarged and the tissue becomes infiltrated with lymphocytes. On the cellular level the mitochondria size is increased. Gradually the liver becomes fibrotic and very often the cirrhosis evolves.

One of the other important issues in alcoholic individuals is the source of their caloric intake. These individuals draw the majority of calories from the caloric rich alcoholic beverages with low nutritive value (the lack of important nutrients and vitamins). Chronic abuse of alcohol depletes the pool of liver proteins which are consumed for energy production and the insufficient intake of proteins only worsens this imbalance. Resulting disturbances in protein and lipid metabolism leads to undernourishment which adversely influences other metabolic pathways, including those influencing the function of the nervous system.

The experimental animal studies suggest that the application of toxic substance may influence the protein metabolism of nerves. After certain toxic compounds (organophosphorus compounds, acrylamide) peripheral neuropathy develops with confirmed protein metabolism disorder. One of the important proteins affected is the neuronal target esterase (NTE), which plays an important role in the development and function of neurons probably by influencing the signal pathways between neuronal and glial cells (Glynn, 2000; Moretto, 2000). The damage to this important enzyme may lead to disturbance of neuronal function and deceleration of axoplasmic flow. Such changes together with the demyelinisation result in a picture similar to Wallerian degeneration -- so called chemical nerve transsection (Glynn, 2000).

The toxic influence of alcohol on cells of the nervous system and of other tissues plays an important part in the development of chronic metabolic disorders. These changes are slow and gradual and only in later stages result in malabsorption and maldigestion. These states further progress to development of undernourishment with associated disturbances of hemopoesis, skin and muscle function, nervous system function and other metabolic disorders (Fig. 2).

Consequently the problem of different influences of alcohol on different part of the nervous system comes into question. While the CNS has its own barrier systems (blood-brain barrier), which may defy the metabolic and toxic influences and their effect on brain functions for a significant period of time, the PNS lacks this protective barrier which can contribute to the fact that PNS disorders are present in 12--30 % of alcohol abusers (Erbsloh, 1967; Scheid, 1980).

Finally genetic factors have to be taken into account. Obviously the genetic conditioned enzymatic defects may cause the dysfunction of nervous system. The decreased tolerance of alcohol ingestion in Asian population is well known. Many works studied the incidence of alcohol abuse in siblings of alcoholics. An increased incidence of alcohol abuse in monozygotic twins compared to dizygotic twins or to adopted children raised in families of alcoholics was observed (Noble, 1996). The genetic association of D2 (dopamine) receptor encoding is mentioned as well.

Should we therefore acclaim the Plutarch and Aristotle who suggested that the alcoholics give birth to children alcoholics (Noble, 1996).

References

Achord JL. Alcohol and the liver. Sci Amer Sci Med 1995; March/ April: 16.

Adams RD, Victor M. Principles of Neurology. Fifth edition. McGraw-Hill Inc., 1993, 1386.

Behse FF, Buchthal F. Alcoholic neuropathy: Clinical, electrophysiological and biopsy findings. Ann Neurol 1977; 2: 95.

Bischhoff A. Die alkoholishe Polyneuropathie. Klinische, ultrastrukturelle und pathogenetische Aspekte. Dtsch Med Wschr 1971; 96: 317.

Dejerine J. Contribution l'étude de la névrite alcoolique (forme paralytique, forme ataxique, tachycardie par névrite du pneumogastrique). Arch Physiol Norm Pathol (Paris) 1887; 3,S,X: 248.

Denny-Brown DE. Neurological aspects of thiamin deficiency. Fed Proc 1958; 17 (Suppl 2): 35.

Dreschfeld J. Further observations on alcoholic paralysis. Brain 1886; 8: 433.

Erbslöh F. Peripheres Nervensystem. Polytope Erkrankunge (Polyneuritid, In: Almanach für Neurologie und Psychiatrie, 1967, Lehmann, München 1967).

Fennelly J, Frank O, Baker H, Leevy CM. Peripheral neuropathy of the alcoholic-aethiologic role of aneurin and other B-complex vitamins. Brit Med J 1964; II: 1290.

Glynn P: Neural development and neurodegeneration: two faces of neuropathy target esterase. Prof Neurobiol 2000, May, 61 (1): 61—74.

Greenfield JG, Carmichael EA. The peripheral nerves in cases of subacute combined degeneration of the cord. Brain 1935; 58: 483.

Hun H. Alcoholic paralysis. Amer J Med Sci 1885; 89: 372.

Jackson J: On a peculiar disease resulting from the use of ardent spirits. New Engl J Med 1822; 2: 351.

Lettsom JC. Some remarks on the effects of Lignum Quassiae. Mem Med Soc Lond 1780; 1: 128.

Ludin HP, Tackman W. Polyneuropathien. Stuttgart--New York, Georg Thieme Verlag 1984, 250—255.

McLeod JG. Alcohol, nutrition and the nervous system. Med J Austral 1992; September 18: 273—274.

Moretto A. Promoters and promotion of axonopathies. Toxicol Lett 2000; March 15: 17—21, 112—133.

Noble EP. The gene that remarks alcoholism. Amer Sci Med 1996, March-April: 52.

Scheid W. Lehrbuch der Neurologie. Vierte Auflage. Stuttgart, Georg Thieme Verlag 1980.

Sluga E. Polyneuropathien, Typen und Diffensierung. Ergebnisse bioptische Untersuchungen. In: Bauer HJ, Gänshirt H, Vogel P (Hrsg): Shriftenreite Neurologie. Berlin, Springer 1974.

Stibler H, Borg S. Carbohydrate composition of transferin in alcoholic patients. Alcoholism: Clin Exp Res 1986; 10: 61—64.

Stibler H, Kjellin KG. Isoelectric focusing and electrophoresis of CSF proteins in ... of different origins. J Neurol 1976; 30: 269—285.

Tomasulo PA, Kater MRH, Iber FL. Impairment of thiamine resorption in alcoholism. Amer J Clin Nutr 1968; 21: 1340.

Varsik P (Ed). Neurológia II. Patogenéza a klinika nervových chorôb. Bratislava Lufema 1999.

Victor M, Adams RD. The effect of alcohol on the nervous system. Res Publ Assoc Res Nerv Merit Dis 1953; 32: 526.

Victor M, Adams RD, Collins GH. The Wernicke-Korsakoff Syndrome. A Clinical and Pathological Study of 245 Patients, 82 with Postmortem Examinations. Philadelphia, FA Davis 1971.

Victor M. Polyneuropathy due to nutritional deficiency and alcoholism. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R (Eds): Peripheral Neuropathy. Second ed. 1899, Philadelphia, W.B. Saunders, 1984.

Victor M, Ropper AH. The Adams and Victors Principles of Neurology. Seventh Ed. McGraw-Hill Inc., 2001, 1692.

Vinken PJ, Bruyn GW. Handbook of Clinical Neurology. Disease of nerves. Vol. 7, part 1. North Holland Publ. Company, 1970, 679.

Received January 18, 2001.
Accepted December 7, 2001.