Alcoholic Neuropathy

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PERIPHERAL nerve disorders are a common sequel of excessive consumption of alcohol. The clinical features and natural history, the etiology and therapy of these disorders will be reviewed.

CLINICAL FEATURES

Alcoholic neuropathy can be defined as a generalized symmetrical affection of the peripheral nerves which commences in the extremities and spreads proximally. The disorder results in weakness and wasting of the muscles most evident at the periphery, with reduced or absent deep tendon reflexes. There is also an impairment of sensation so that there is a decreased ability to appreciate the vibrations of a tuning fork, the movements of the joints, the pain of a pinprick, and light touches on the skin. The sensory disorder is first detectable on the toes and fingers and later spreads up the limbs to produce a generally symmetrical and bilateral "glove and stocking" hypalgesia and hypesthesia.

The clinical characteristics, although presenting as a continuum, can be considered in three stages as this disease has a slow evolution. In the first instance, an aching discomfort and fatigue appear in the anterior tibial muscles on walking. As time passes, walking even shorter distances brings discomfort, painful cramps, and occasional paresthesias in the feet. These symptoms often persist for months. Examination of the patient at this time will reveal few abnormal signs: a little weakness of extension of the toes and ankles, some atrophy of the leg muscles with absent or reduced ankle jerks, and inability to appreciate the vibrations of a tuning fork at the ankle, and fine movements of the toes.

If untreated, the first symptoms intensify and extend from the feet to the legs, and the hands may become involved. The weakness of the ankles is so marked that foot drop renders the gait abnormal. Appreciable wasting of the leg muscles accompanies the weakness, and the knee and ankle reflexes are absent or sluggish. Weakness of the intrinsic hand muscles may be evident and the radial reflex may be sluggish. The patient complains of a persistent burning and coldness of the feet, and the finger tips feel tingling, rough, or numb. There is an inability to discriminate between two points on the finger tips along with some dullness of pain. Cutaneous sensibility is abnormal on the feet gradually merging with the normal below the knee. The disorder of position sense in the toes is marked, and a vibrating tuning fork is not felt at the shin.

Finally, in the severely affected patient, the legs are almost paralyzed and the hands are useless, the flabby muscles are tender to compression and fibrous contractures further limit mobility. All the deep tendon reflexes are absent. All forms of sensation are markedly impaired at the periphery so that a "glove and stocking" hypesthesia and hypalgesia or even anesthesia is produced. At the same time, a distortion of deep pain or pressure sensitivity may be present so that both light touch or pressure produces extreme discomfort. The peripheral fibres of the autonomic nervous system are also affected, and autonomic dysfunction is manifested by excessive perspiration of the instep and dorsum of the feet and on the finger tips; the skin is

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described as feeling cold and clammy. Less frequently the skin is dry, glossy and atrophic, the nails ridged, pitted and brittle. It was this advanced stage of the disease which featured in the classic descriptions of Lettsom[1] in 1787, and Jackson[2] in 1822.

Lettsom described the state of the patient vividly. "The appetite for food vanishes but sometimes continues voracious; and, at the same time whilst the body is costive, and no vomiting ensues, the lower extremities grow more and more emaciated; the legs become as smooth as polished ivory, and the soles of the feet even, glassy, and shining, and at the same time so tender, that the weight of the finger excites shrieks and moaning and yet, I have known, that in a moment's time, heavy pressure has given no uneasiness. The legs, and whole lower extremities, lose all power of action; wherever they are placed, there they remain till moved again by the attendant; the arms and hands acquire the same paralysis, and render the patients incapable of feeding themselves."

Just as the disease develops slowly so recovery is a gradual process. The most recent symptoms and signs are the first to clear whereas the earlier signs may change only very slowly. The loss of vibration sense of the ankles and the absent ankle jerks may persist as a permanent legacy of the illness.

However, the clinical findings in many cases of multiple neuritis do not conform to the conventional descriptions and the disorder is subject to great individual variation. Patients are encountered who have been troubled by an uncomfortable numbness of the feet for many months and in whom no evidence of weakness is found. In others, loss of the sense of the position of the joints with resulting ataxia may be the predominant disability. In still others, weakness and foot drop may be virtually the sole disability. Unilateral or asymmetrical neuropathies are sometimes encountered in chronic alcoholics. Dysfunction in the areas supplied by the musculospiral or peroneal nerve is most commonly observed. Cases have been recorded in which the supinator longus and the extensor metacarpal of the thumb were spared while the rest of the muscles innervated by the musculospiral nerve were severely paretic. Oppenheim[3] believed that the disorder was sometimes limited to individual nerves. He had observed patients with peroneal nerve palsies in whom tibialis anticus was spared. Sometimes the extensor communus digitorum was the only muscle affected, in such cases the paraesis were almost always symmetrical. While many of these asymmetrical peripheral disturbances may be attributable to pressure, a general metabolic etiology has not been excluded.

Rarely, cranial nerve palsies may be encountered in chronic alcoholism. These palsies are usually bilaterally symmetrical, but isolated palsies are sometimes met with. The seventh nerve is most frequently involved, the external ocular motor nerves less often. Pupils which are irregular and sometimes unreactive to light are found in alcoholics in the absence of any clinical or laboratory evidence for a syphilitic etiology. It should be borne in mind that in the absence of signs of generalized peripheral neuropathy, isolated cranial nerve palsies occurring in alcoholics may not be manifestations of a general metabolic defect.

Visual failure, with bilateral central scotomas, is occasionally encountered, and demyelinization of the optic nerves has been described. Most patients reveal some degree of mental change: their memory is poor, they have poor orientation, a decreased attention span, and lack of concentration; formal testing confirms an early dementia. The Korsakoff type of psychosis is much less frequently encountered than are mild defects of mentation. Along with these mental changes, the well recognized association of neuropathy with Wernicke's encephalopathy further confirms the fact that the central nervous system does not escape unscathed. The earlier writers do not allude to lesions of the spinal cord, but we have encountered several chronic alcoholics with peripheral neuropathy and unequivocal signs of corticospinal tract disease. In these patients a clinical diagnosis of subacute combined degeneration of the cord has failed to be substantiated by hematologic and radioactive cobalt studies.

Greenfield and Carmichael[4] found demyelinization of the peripheral nerves in alcoholic polyneuritis. Evidence of axis cylinder destruction was found at a variable time following the onset of the demyelinizing process. Zimmerman[5,6] made a study of the pathologic changes and found no evidence of an active inflammatory cellular reaction at any stage of the disease. Nonne[7] has described a loss of myelin in the dorsum and lateral columns of the spinal cords of chronic alcoholics, and he pointed out the close similarity superficially which these lesions had to those of combined system disease. Other writers[8–11] also report the occurrences of spinal cord lesions involving the long tracts of both the lateral and posterior columns. Similar changes have been encountered with peripheral neuropathy in the nutritional disorders of the severely malnourished.

The diagnosis of peripheral neuropathy does not usually present any difficulty, and the cause is usually so obtrusive that a diagnosis of alcoholic neuropathy may become inevitable. There is a danger of making a diagnostic error by attributing every neuropathy in an alcoholic to his way of life when other factors may well be responsible. Walshe[12] has emphasized the uniformity of the clinical picture of neuropathy despite the diversity of the causative factors and has said that there are no qualitative differences between the various types of peripheral neuropathy.

Different features have in the past been considered of value in the differentiation of alcoholic neuropathy from other neuropathies. Wilson[13] believed that the presence of increased sensitivity to deep pain and pressure was suggestive of alcoholic neuropathy, although he emphasized that it was not pathognomonic. Granger Stewart[14] was of the opinion that alcoholic neuritis could be recognized by the prominence of certain symptoms, namely, the severity of pain and cutaneous paresthesias, the tender muscles, the involvement of the lower limbs, the peripheral distribution of the symptoms and the prominence of involvement of the extensor muscles. Unfortunately, any or all of these symptoms may be present in neuropathies as diverse as those found in diabetes mellitus, polyarteritis nodosa, or infectious polyneuritis. Many writers have stressed the value of mental deterioration in the differentiation of alcoholic neuropathy from other neuropathies, and our experience supports this view.

Further, the nutritional and toxic neuropathies as a group rarely involve the proximal muscles of the limbs or the trunk musculature, and when both proximal and distal muscles are weak, the distal ones will always be found most severely affected. In general, however, it is wise to bear in mind that in individual cases there are no pathognomonic features which allow alcoholic neuropathy to be discriminated from neuropathy arising from other causes. In many cases stigmata of chronic alcoholism are encountered, the unkempt appearance and general tremulousness are striking. Nausea, vomiting, and abdominal discomfort suggesting gastritis or the signs of portal cirrhosis may be found. The disease is a general metabolic one, and substernal discomfort, tachycardia, and electrocardiographic abnormalities point to an accompanying cardiac abnormality.

ETIOLOGIC CONSIDERATIONS

Many authors[12,15,16] have emphasized that alcoholic neuropathy is a bilaterally symmetrical affection and imply that this symmetry involves the peripheral nerves in a generalized and nonselective fashion; this suggests a metabolic defect in its causation.

Neuropathy appears to be found in 3 to 20 per cent of patients admitted to the hospital with chronic alcoholism.[17] The figures from different institutions vary according to the criteria for selection of cases for admission. Formerly considered to be primarily a disorder of females, the great bulk of the cases today is found in males; this change in incidence is probably attributable to a change in social customs, rather than to any alteration in the incidence of the disease. Victor and Adams[17] have shown that the incidence of neuropathy in female alcoholics is higher than in males.

Gowers[18] and Oppenheim[3] were both struck with the importance of cold as a precipitating factor, and a higher incidence of neuropathy is found during the winter months. Inter-

current disease, bronchitis, and influenza are more common in colder weather, and it seems that the appearance of any infection in an alcoholic may be associated with the development of neurologic symptoms. Tuberculosis has this association to a marked degree, and a period of unaccustomed exertion or an attack of vomiting or of diarrhea may be followed by paresthesias or foot drop in a chronic alcoholic who was formerly symptom-free. It is easy to see why these agents were all held to be responsible for neuropathy in the past, whereas today they are known to increase the vitamin requirements and exaggerate a mild deficiency.

Physicians had always been perplexed by the question: "If alcohol or one of its metabolites was the toxic agent responsible for the generalized neuropathy, why then should neurologic damage develop in such a small percentage of chronic alcoholics?" With knowledge that beriberi was a deficiency disease, curable by the administration of vitamins, it was not long before Shattuck[19] postulated that alcoholic polyneuropathy might have a similar etiology. Wechsler,[20] after a careful comparison of the characteristics of beriberi and alcoholic neuropathy, came to the same conclusion. Minot, Strauss and Cobb[21] examined a number of alcoholic patients with respect to deficiency disease. They experienced great difficulty in assessing the diet of these patients because of the unreliable dietary histories. They came to the conclusion that most of their patients had had an inadequate diet for a considerable time.

In general, chronic alcoholics spend less money on food than nonalcoholics and the association of anorexia with excessive drinking is well known. The inadequacy of the diet may be enhanced by additional factors. Jolliffe et al.[22] have drawn attention to the intake of "vitamin free" calories in the form of alcohol. The disturbance in the ratio of vitamins to calories in the diet which results may render a barely adequate diet inadequate in vitamins.

Strauss[23] has discussed the importance of a gastrointestinal disorder in conditioning a deficiency disease. The great frequency of achlorhydria in chronic alcoholics may be of importance.[24] Blotner[25] has described the inhibition of proteolytic gastrointestinal enzymes by alcohol.

The part which cirrhotic liver disease may play remains uncertain, although Wayburn and Guerard[26] found a high association between neuropathy and cirrhosis.

The proof that dietetic factors are intimately concerned with the appearance of neuropathy was obtained by Strauss,[27] who maintained ten chronic alcoholics with peripheral neuropathy on their usual whiskey intake and supplemented their diet with vitamins administered parenterally and orally; in all patients the polyneuropathy improved. Blankenhorn and Spies[28] carried out a similar experiment with patients suffering from "alcoholic neuritis," and "alcoholic pellagra and neuritis." When given whiskey and a good diet they also improved.

For the sake of convenience the various dietary factors which may be implicated will be discussed in turn.

Thiamine has long occupied a central place in any discussion on the causation of alcoholic neuropathy. There is no doubt that thiamine is essential for the normal metabolism of nervous tissues. Peters[29] has shown that it is concerned in the release of energy from carbohydrate, and, as co-carboxylase, it is concerned with the oxidation of α-keto acids. In the absence of thiamine both pyruvate and pyruvic aldehyde accumulate, and with a high carbohydrate diet this accumulation is increased. Sinclair[30] has suggested that it is the accumulation of these toxic metabolites which produces the anorexia of thiamine deficiency. In thiamine deficiency the neurone may be disorganized either through its own inefficient metabolism or through the accumulation of toxic metabolites. However, attempts to produce thiamine deficiency in man,[31–33] have been hampered by the difficulty of restricting the deficiency to thiamine alone. Objective signs of neuropathy have seldom been observed and when substitution therapy was instituted the preparations given usually included several vitamins. In experimental animals changes in peripheral nerves do

develop in thiamine-deficient birds. In mammals it has been more difficult to produce experimental neuropathy, and it was not established until Sinclair and North[34] produced a peripheral nerve degeneration in rats on a thiamine-deficient diet. Thiamine is deficient in the diets of chronic alcoholics, and it is possible that in the presence of gastrointestinal disease its absorption may be impaired or that the vitamin may be inactivated. Further, in the presence of liver disease, the phosphorylation of thiamine in that organ may be inadequate.

The excretion of thiamine in alcoholics with neuropathy is subnormal.[35] Often, however, the alcoholic neuropathy does not improve strikingly with thiamine treatment alone, and Meiklejohn[36] seriously doubted whether this vitamin had any etiologic relationship. Walshe[37] has expressed similar views and Brown[38] found that patients with alcoholic neuropathy treated with thiamine left the hospital no sooner than patients treated with good diet alone.

Pantothenic acid is a part of coenzyme A and is also concerned with the oxidation of pyruvate.

Experimental pantothenic acid deficiency in swine has produced a peripheral neuropathy.[39] In man, Bean and Hodges[40] have given an analogue of pantothenic acid to volunteer subjects producing symptoms of peripheral nerve disease. This vitamin is extremely widely distributed in nature, and there is no evidence that it is deficient in chronic alcoholics.

Lipoic acid: The pyruvate oxidation system can be disordered in another way in chronic alcoholics if the production or catalytic function of lipoic acid is disrupted.

Sinclair[30] has stressed the importance of this substance in metabolism and has drawn attention to the fact that, as it is probably formed in the liver, production may be defective in a chronic alcoholic. A deficiency of lipoic acid may be produced by the formation of stable compounds with excessive pyruvate or the acetaldehyde formed during the breakdown of alcohol. Vitamin B_{12} may be concerned in the oxidation and reduction of lipoic acid, and a deficiency of vitamin B_{12} could occur in alcoholics.

Finally it is of interest that the neuropathy of chronic alcoholics treated with Antabuse® may be due to this chemical, blocking or combining with lipoic acid.

Pyridoxine: A deficiency of pyridoxine in the diet of swine has been shown to produce peripheral neuropathy,[39] and in man the antagonist desoxypyridoxine has produced peripheral neuritis.[41] The importance of this vitamin in the maintenance of a normal peripheral nervous system has been clearly shown by its use in the prevention and treatment of neuropathy occurring in patients receiving isoniazid therapy for tuberculosis.

Spies[42] found that in several patients with alcoholic neuropathy, who had not completely responded to treatment with nicotinic acid and thiamine, the neuropathy cleared up rapidly after pyridoxine was administered.

Riboflavin and nicotinic acid are known to be essential for the integrity of the nervous system. Alcoholics have been described with the clinical stigmata of riboflavin deficiency. The administration of the specific vitamin relieves the skin lesions, whereas the neuropathy is unaltered.[43] In nicotinic acid deficiency both the mental disturbance and the skin lesions clear rapidly following the administration of the specific vitamin, leaving the peripheral neuropathy unaffected.[44,45] On the basis of this evidence these vitamins have been thought to play no part in the causation of peripheral neuropathy. This argument, however, is not necessarily valid as there is good evidence that once morphologic changes in the peripheral nerves have occurred recovery may be very slow.

Vitamin B_{12} deficiency may produce peripheral neuropathy, and the presence of achlorhydria and gastrointestinal disorders in alcoholics render a defect in vitamin B_{12} absorption possible. There is no record of vitamin B_{12} deficiency in chronic alcoholics, although it seems quite possible that this may occur.

Vitamin C: Wortis et al.[46] have shown that chronic alcoholics with peripheral neuropathy may be deficient in this vitamin. They drew

attention to the fact that mental and neurologic signs are rare in scurvy and that scurvy seldom develops in alcoholics nor does alcoholic neuropathy respond to therapy with vitamin C.

Vitamin A: Mellanby[47] has found peripheral neuropathy in experimentally induced vitamin A deficiency. But there is no evidence that this vitamin is deficient in the chronic alcoholic patient.

Inanition: Several authors have reported peripheral neuropathy in animals given adequate amounts of vitamins but deficient in both calories and protein. The role played by the essential amino acids in the nutrition of the nervous system is quite unknown. It may well be that deficiency of these and other factors is also involved in the production of alcoholic neuropathy. The chronic alcoholic is almost always deficient in many different vitamins as well as other nutritional elements. The combination of these various factors may be more dangerous to the nervous system than the absence of any single substance, and these deficiencies may render individual nerves more susceptible to injury by other agents such as physical trauma.

TREATMENT

In the present state of knowledge it is impossible to be dogmatic about the treatment of alcoholic neuropathy. There is evidence that treatment with thiamine alone is not always satisfactory and Romano[48] found 6.4 per cent of patients with chronic alcoholic neuropathy did not respond to thiamine therapy; 32.4 per cent improved slightly, while the remainder improved markedly and were considered cured. Jolliffe[49] demonstrated that, in general, patients responded best to massive doses of thiamine and the speed of recovery was directly related to the amount of vitamin administrated. Because of the multiple deficiencies usually present in chronic alcoholics, there would seem to be good grounds for giving multivitamin preparations rather than single crystalline substances.

In the first week vitamins in ten times the normal daily requirement should be given, and thereafter about half this amount should be administered. There is very good evidence, both theoretic and clinical, for believing that a good mixed diet may be of equal value to the administered vitamins.

In the acute stage of the illness there is some evidence that brisk exercise may be harmful. Passive movements are important from the onset to prevent fibrous contractures and limitation of joint mobility. Voluntary activity should be postponed until the patient is convalescent.

On the regimen of parenteral vitamins, a good diet and bed rest almost all patients with alcoholic neuropathy recover, those with moderate severity in six to eight weeks, those with more serious involvement after a somewhat longer period.

CONCLUSION

In discussing this subject of alcoholic neuropathy I have attempted to draw the distinction between those facts which have been definitely established and those which are merely conjectural. The clinical characteristics of this disorder are now well known and clearly demarcated.

It is perhaps surprising that so much obscurity surrounds the precise etiologic agents. The time has arrived when a reappraisal of the nutritional factors and therapy of alcoholic neuropathy should be made.

REFERENCES

Because of the author's transfer to an overseas post, the references for this article were not received in time for publication. However, they will appear in the author's reprints.