Management of alcohol withdrawal symptoms

The current epidemic of alcoholism shows no sign of abating, and with 20-30% of hospital patients currently thought to be excessive drinkers, doctors are likely to have to deal increasingly with the alcohol withdrawal syndrome.

Dependent drinkers react in different ways to the sudden withdrawal of alcohol, so that even if an individual's drinking habits are known he may respond by habits more difficult to predict. Some people seem to be scarcely affected, while at the other end of the scale a few, put at less than 5% of the total, develop the dramatic features of delirium tremens, especially if they are also stressed by infection, injury, or operation. Most display some features of anxiety, agitation, tremor, and sweating, accompanied by fever, nausea, and retching. The general hyperactivity is often associated with varying degrees of insomnia, itching, cramps, hyperacousis and tinnitus, and perceptual disturbances; and both tachycardia and hypertension are common. Confusion, paranoia, visual hallucinations, and convulsions occur in the more severely affected patients. Gross and his colleagues have devised a method of grading withdrawal symptoms by a series of scales, which can be used for comparative studies and for assessing different treatments.

Symptoms begin six to eight hours after the last drink (which explains why the chronic alcoholic steady the nerves with the early morning drink), reach a peak at about 48 hours, and then subside over the course of a week. Their cause is not known. Increased secretion of sympathomimetic and other amines has been suggested to explain the hyperactivity, and though the adrenal cortex is overactive (as shown by raised plasma concentrations of cortisol) the response to stress seems to be inadequate. The dehydration and oliguria found in the early phase of withdrawal possibly result from the chronic diuresis caused by alcohol or from increased secretion of antidiuretic hormone. Hypokalaemia may be prominent in severe forms of withdrawal.

Management requires sympathetic handling and careful observation. If possible patients should be treated in a general medical ward, even though they tend to be disruptive. The cause of the syndrome should be established, infections such as pneumonia being the most common, and treated vigorously. If necessary an intravenous drip should be set up to combat dehydration and to facilitate the giving of sedatives. For the first day or two additional supplements of 50-100 mmol potassium should be given in divided doses, and injections of a high-potency vitamin preparation are said to be beneficial. Over 100 drugs have been tried in the treatment of withdrawal symptoms, and the choice is often dictated by personal preference. The current favourite in Britain is chlormethazol in a dose of 500-1500 g every six hours initially; the aim should be to reduce the dose as symptoms disappear and to stop the drug as soon as possible to avoid dependence. Chlordiazepoxide is a useful alternative and may need to be given in large doses at first—for example, 25-50 mg every six hours; cumulative effects can be avoided by reducing the total amount by a quarter each day. Both drugs will suppress anxiety and prevent convulsions. If convulsions do occur chlordiazepoxide is the drug of choice; phenytoin does not act quickly enough. Beta-blocking agents, such as propranolol 40 mg six-hourly, have been used to treat the hyperactivity, but they will not prevent convulsions and do not augment the action of sedatives.

Since the symptoms arise because of the sudden withdrawal of alcohol, treatment is sometimes advocated with small quantities of alcohol. The equivalent of about 8 g absolute alcohol, (half a pint of beer or a glass of spirits) can be given every four to six hours and gradually tailed off; it has the advantage of being safer than drugs and allows the latter to be used in smaller quantities. Alcohol is also a valuable preventive agent in known alcoholics who are undergoing an operation, for example; and it can be tried as a first step in the patient who unexpectedly becomes confused or delirious while in hospital.

Multiple sclerosis in the Orkney and Shetland Islands and in north-east Scotland

Sutherland reported that multiple sclerosis in 1954 appeared to be more common in the Orkney and Shetland Islands and in Caithness in the north-east of Scotland than in the west of Scotland, and postulated that there might be a disadvantageous genetic factor responsible for this high prevalence. Since then three further studies of the prevalence of multiple sclerosis, based on prevalence days in 1962, 1970, and 1974, have been undertaken in the Orkney and Shetland Islands, the last two by Poskanzer and his colleagues. The population of each group of islands had varied slightly between 17 000 and 20 000 people; and the prevalence of ascertained cases of multiple sclerosis increased during 1954-74 from 82 to 258 per 100 000 (from 17 to 45 patients) in the Orkney Islands and from 118 to 152 per 100 000 (from 22 to 28 patients) in the Shetland Islands. Other studies have also shown that repeated
intensive surveys of multiple sclerosis yield a higher prevalence in each subsequent survey.10,11 Twenty-six patients with probable multiple sclerosis were eventually found, in the Orkneys and 14 in the Shetlands whose disease had started before 1954 but who had not been included in the 1954 survey (most of the cases not having been diagnosed). During the 20 years (1954–74), moreover, the mean interval from onset to diagnosis fell slightly from 7.5 to 5.2 years, which suggests that a substantial number of undiagnosed patients remain in the community. The median duration of the disease, calculated by doubling the time from onset to prevalence day, increased from 26 to 40 years in the Orkneys and from 24 to 34 years in the Shetlands—evidence that an increase in survival has contributed considerably to the increase in prevalence.

Shepherd and Downie have undertaken two studies in a population of about 440 000, divided into 28 small populations, in north-east Scotland, in and around Aberdeen, based on data for 1970 and 1974.12,13 As in other surveys, the second survey showed a higher prevalence of multiple sclerosis than the first. The prevalence in each of the subareas varied greatly by chance, and four areas had a prevalence as high as or higher than was found in the latest (1974) study in the Shetland Islands. Only in the last Orkney study does the prevalence of probable and possible multiple sclerosis exceed the prevalence in all the 28 subareas on the mainland.12,13 There is no difference in the reported death rates of multiple sclerosis in north-east Scotland and in the rest of Scotland, suggesting that its prevalence does not differ greatly between the east and west of Scotland.

The high prevalence of multiple sclerosis found in the Orkney and Shetland Islands is therefore partly due to the intensive and prolonged search for multiple sclerosis in small populations that have an excellent medical service with a high awareness of the disease (interestingly, the highest reported prevalence of multiple sclerosis in the United States is in Rochester, Minnesota, a town that includes the Mayo Clinic).10 But a “founder effect” may also play a part: the populations of these islands probably originate from a few early settlers, mainly Norsemen, one or more of whom could have had a strong genetic predisposition to multiple sclerosis; and his descendants could be responsible for a relatively high frequency of such a genetic predisposition.

Certainly multiple sclerosis appears to have a genetic element. It is more common than could be expected by chance in two members of the same family; and it appears to be associated with certain HLA blood groups, at least according to some studies. But there is undoubtedly an environmental factor because, for instance, immigrants from Europe to South Africa or Israel who immigrate in childhood have less risk of multiple sclerosis than those who immigrate as adults.14,15 The world pattern of prevalence—common in Europe, uncommon in Asia and Africa—is similar to that of adult paralytic poliomyelitis before the introduction of the Salk and Sabin vaccines, suggesting that the environmental factor could well be a virus.16 The immunological changes in the cerebrospinal fluid—increased immunoglobulin G, suggesting impaired ability to eliminate an infection—also support this view.

In the Faroe Islands multiple sclerosis is reported to have increased since the arrival of the British during the last war, and one hypothesis has been that they introduced a new virus with their dogs.17 Poskanzer and his colleagues looked intensively for an environmental factor in the Orkney and Shetland Islands and found a remarkable similarity between the patients with multiple sclerosis and controls for diet, social class, occupation, housing, exposure to animals, schooling, travel, infectious diseases, and other aspects of medical history. Minor differences, however, were noted for sanitation, place of residence at the onset of the disease, and exposure to animals, which give some additional support for an environmental factor in multiple sclerosis.3 The frequency of HLA haplotypes A3, B7, and DW2 in the patients and controls was compared, but no significant difference was found—in contrast with the findings in other studies, where these haplotypes have shown an increased frequency in patients with multiple sclerosis.18,19 No consistent pattern of raised antibody titres or presence or absence of antibody was noted in patients compared with the control groups.9 Patients had had common childhood infections, including measles, at a later age than inhabitants of Europe and the United States—six patients indeed had measles after they had developed multiple sclerosis. The HLA factor B7 was significantly correlated with high titres of measles antibody in healthy controls; and controls with haplotype B7, DW2, and B-cell 4 had significantly higher titres of measles and rubella antibody than controls without these determinants.8 This suggests that in normal people viral antibody titres are influenced by certain HLA antigens, which is evidence that another, as yet undefined, determinant in the HLA complex may govern the immune response in multiple sclerosis. Migration made at most a minor contribution to the high prevalence of multiple sclerosis.7

Studies of multiple sclerosis among different populations and among people who have moved from one environment to another can throw light on genetic and environmental factors. Often such studies can best be undertaken in the relatively closed communities of islands such as those of northern Scotland and the Faroe Islands. In the Hawaiian islands multiple sclerosis is common among the Caucasian but relatively rare among the Japanese, in whom the disease often takes the acute form of neuromyelitis optica (Devic’s syndrome).20 Islands in the southern Mediterranean are at the junction of high and low prevalence: multiple sclerosis is common in Sicily but very uncommon, 4 per 100 000, in neighbouring Malta.21,22 The studies of multiple sclerosis in the Orkney and Shetland Islands are a good illustration of how genetic and environmental factors that might be responsible can be investigated by close collaboration between epidemiologists and workers in disciplines such as immunology and virology.

10. Percy AK, Nobrega FT, Okazaki H, Glatte E, Kurland LT. Multiple sclerosis and controls for diet, social class, occupation, housing, exposure to animals, schooling, travel, infectious diseases, and other aspects of medical history. Minor differences, however, were noted for sanitation, place of residence at the onset of the disease, and exposure to animals, which give some additional support for an environmental factor in multiple sclerosis.3 The frequency of HLA haplotypes A3, B7, and DW2 in the patients and controls was compared, but no significant difference was found—in contrast with the findings in other studies, where these haplotypes have shown an increased frequency in patients with multiple sclerosis.18,19 No consistent pattern of raised antibody titres or presence or absence of antibody was noted in patients compared with the control groups.9 Patients had had common childhood infections, including measles, at a later age than inhabitants of Europe and the United States—six patients indeed had measles after they had developed multiple sclerosis. The HLA factor B7 was significantly correlated with high titres of measles antibody in healthy controls; and controls with haplotype B7, DW2, and B-cell 4 had significantly higher titres of measles and rubella antibody than controls without these determinants.8 This suggests that in normal people viral antibody titres are influenced by certain HLA antigens, which is evidence that another, as yet undefined, determinant in the HLA complex may govern the immune response in multiple sclerosis. Migration made at most a minor contribution to the high prevalence of multiple sclerosis.7

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Angiosarcoma of the liver: A growing problem?

Angiosarcoma of the liver, otherwise called Kupffer-cell sarcoma or malignant haemangioendothelioma, is rare: fewer than 200 such tumours have been reported world wide. It usually occurs in the sixth and seventh decades and is more common in men than in women. Angiosarcoma is often multifocal, arising in a scarred or cirrhotic liver, and consists of malignant endothelial cells supported on a reticulin framework. In some areas tumour cells make a homogeneous tumour, while in others the hepatic cell plate structure is still present, though compressed, and dilated sinusoids are lined by malignant endothelial cells.

Angiosarcoma is one of the cancers with an identified cause: thorotrast, arsenic, and vinylchloride have all been clearly implicated. Thorotrast, a colloidal preparation of thorium dioxide, was used as a radio-opaque contrast medium between 1928 and the mid-1950s. \(^1\) When given intravenously more than 70% of the dose is taken up by the liver, and the mean radiation dose received by the liver varies between 1000 and 3500 rads. Tumours appear 12 years or more after exposure, and in a review of 123 thorotrast-induced tumours \(^3\) there were 41 angiosarcomas, 40 cholangiocarcinomas, 24 hepatocellular carcinomas, and 18 other carcinomas. Though thorotrast has not been used for about 25 years, new cases are still appearing. The peak incidence may now be passed, \(^4\) but a sizeable population of recipients are still alive, and their accumulated radiation dose from retained thorotrast is still increasing. Chronic arsenical intoxication has long been recognised as a cause of liver fibrosis, cirrhosis, and angiosarcoma. It was an occupational disease among vinters in Moselle \(^5\) and was seen in patients given prolonged treatment with Fowler's solution or potassium arsenite. \(^6\) In Britain the use of arsenic in pesticides has diminished considerably since 1960 and the use of arsenical drugs was largely discontinued after 1950.

Polyvinylchloride is formed by polymerisation of liquid vinylchloride monomer. Commercial production began in the 1940s, and the industry has grownprodigiously; current British production is around 400,000 tons per annum. Polyvinylchloride is used in a mass of different products, ranging from piping to credit cards. Monomer can leak out of polyvinylchloride in tiny amounts, and, while this probably poses no threat to the general public, last year the United States Food and Agriculture Administration banned the use of polyvinylchloride in food containers. The main risk, however, lies with the workers in the manufacturing industry, and was very high in those cleaning the autoclaves, who were exposed to concentrations of monomer fumes as high as 10,000 ppm. Liver disease and acro-osteolysis (thinning of the bones in the hands and feet) were first noted in Russia and Eastern Europe in the 1950s and 1960s, some time before similar observations were made in Western Europe and North America. The oncogenic potential of vinylchloride was first shown in studies in animals in 1971, \(^7\) and subsequent work showed that exposure of rats to 50 ppm for four hours daily five days a week for one year was sufficient to induce tumours. \(^8\) The first human case of angiosarcoma was reported in the vinylchloride industry in 1974. \(^9\) Since then safety regulations have been progressively tightened, so that the maximum permissible eight-hour average is now 10 ppm with a ceiling of 30 ppm. The latent interval between first exposure and diagnosis of the tumour lies between 12 and 29 years, and—as with the recipients of thorotrast—more cases seem likely to come to light with time.

Most patients with angiosarcoma of the liver present with abdominal pain and swelling with loss of weight. \(^10\) Enlargement of the liver is almost invariable, and ascites is common; the ascitic fluid is often bloodstained. Patients exposed to vinylchloride may also have acro-osteolysis. Laboratory findings are non-specific, but thrombocytopenia is common and microangiopathic haemolytic anaemia and consumption coagulopathy have been reported. \(^11\) The prognosis is grim: 22 of 55 patients died within three months, and all were dead within one year. \(^1\) The only hope of cure lies in transplantation or resection, but the latter is seldom possible since the tumour is usually widespread in both lobes and there is often underlying cirrhosis.

What is the size of the problem in Britain? A register of cases was set up in 1974, and the second report has just been published. \(^11\) Between 1963 and 1977 a total of 35 cases were found acceptable to the panel of histopathologists, and the number of cases seen annually has risen in the last two years. A known cause or agent was identified in only 10 cases—eight due to thorotrast and two to vinylchloride. There was possible exposure to vinylchloride in four other cases, and the survey also suggested an excess of cases in the electrical industry. How many patients will develop angiosarcoma over the next two decades due to prior exposure to thorotrast or vinylchloride is unknown. Nevertheless, doctors should be alert to this possible diagnosis in those with the appropriate history.

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