



MINI-SYMPOSIUM: NEUROPATHOLOGY

Alcohol and the nervous system

Yazan Alderazi, Francesca Brett*

Department of Neuropathology, Beaumont Hospital, P.P. Box 1297, Beaumont Road, Dublin 9, Ireland

KEYWORDS

Blood alcohol concentration;
Central pontine myelinolysis;
Dementia;
Foetal alcohol syndrome;
Marchiafava–Bignami disease;
Morel's laminar sclerosis;
Subdural haemorrhage;
Trauma;
Wernicke's encephalopathy

Summary Alcohol is a substance that impacts the social, psychological, medical, economic and religious spheres of our existence. It is part of every society. Alcohol in moderation can be beneficial. Alcohol abuse mediates its effects both on the developing and the developed brain, directly or indirectly, and has acute and chronic complications. Damage to the developing brain can result from alcohol consumption in pregnancy. Misuse of alcohol in adults can affect both the central and the peripheral nervous system. Direct effects arise due to the toxic and intoxicating effects of alcohol. Nutritional deficiencies are thought to mediate most of the indirect effects of alcohol, as patients with alcohol dependence tend to eat less and derive most of their caloric intake from the alcoholic beverages they consume. Alcohol-related disease places a burden on our health-care systems. In this review, we examine the pathological effects of alcohol on the nervous system.

© 2007 Elsevier Ltd. All rights reserved.

Introduction

Alcohol in the form of ethanol is probably the commonest 'recreational drug' in Western societies. It is estimated that approximately 90% of people consume it at some stage and 30% develop alcohol-related disorders.¹ Alcohol consumption in moderation can have beneficial effects.^{2,3} Problems arise when it is abused. Alcohol dependence (alcoholism) is observed in some 10% of men and 3–5% of women. An additional 5–10% of each sex develop persistent

but less intense problems that are diagnosed as alcohol abuse.¹ Patterns of drinking are changing worldwide with more females and young people drinking excessively, and up to 10% of females continuing to drink during pregnancy.⁴ Adolescents are vulnerable to the memory impairing effects of alcohol but less sensitive to its sedative and motor-impairing effects, which may partially explain the high preponderance of young adults in fatal accidents.⁵ Although it is known that alcohol is implicated in a high proportion of fatal accidents and suicides, interpreting blood alcohol concentrations (BACs) in autopsy samples can be difficult.⁶

This paper will discuss the effects of alcohol on the developing nervous system. The acute and

*Corresponding author. Tel.: +353 1 809 2631;
fax: +353 1 809 2955.

E-mail address: francescabrett@beaumont.ie (F. Brett).

chronic, direct and indirect effects of excess alcohol consumption on the adult nervous system will then be addressed.

Alcohol and the developing nervous system

Foetal alcohol syndrome (FAS) (growth retardation, distinct facial appearance and central nervous system (CNS) dysfunction) is not the only outcome resulting from prenatal alcohol exposure. The term foetal alcohol spectrum disorder (FASD) was adopted as an umbrella term to describe the range of effects that may arise in an individual exposed to alcohol in utero.⁷ The amount of alcohol reaching the developing embryo is a major factor, determined in part, by dose and pattern of alcohol exposure. Not all individuals exposed to similar amounts of alcohol have the same outcome. Other factors are equally important, i.e. genetic (affecting the metabolism and functional sensitivity to alcohol), nutritional (influencing blood alcohol levels), age of the mother and time of exposure (first trimester—migration and proliferation problems).⁷

Alcohol and the developed nervous system (Table 1)

Direct effects (acute)

Memory

Blackouts are episodes of amnesia thought to be due to a rapid rise in BAC. The mechanism is thought to be a block in the transfer of information from short-term memory to long-term storage. Potentiating factors include drugs such as benzodiazepines and marijuana. During these episodes individuals are able to function appropriately, carrying out conversations and other activities. The memory impairment is anterograde. There are two types. *En bloc blackouts* are those where individuals cannot remember any of the events that took place while under the influence of alcohol. These memories do not return even with memory cues. The onset of the blackout is clear and after the events are carried out the individual typically falls asleep; with his/her first full memory being waking up. *Fragmentary blackouts*, i.e. partial blackouts are episodes of impaired memory for some events or details during a session of drinking. These are more common than the en bloc type. Memory blackouts were initially characterized in alcoholics, but can occur with social drinking.^{8,9}

Table 1 Alcohol and the nervous system.

1.	Developing nervous system Foetal alcohol syndrome
2.	Developed nervous system
	Direct effects
	Acute
	Memory loss
	Trauma
	Chronic
	Withdrawal
	Cerebral atrophy
	Dementia
	Cerebellar degeneration
	Central pontine myelinolysis
	Marchiafava–Bignami disease
	Morel's laminar sclerosis
	Hepatocerebral degeneration
	Neuropathy and myopathy
	Indirect effects—nutritional
	Wernicke–Korsakoff psychosis (thiamine deficiency)
	Alcoholic pellagra (niacin deficiency)
	Toxic polyneuropathy
	Optic neuropathy ('tobacco alcohol amblyopia')

The effect of alcohol on neural mechanisms has not been fully elucidated. In rats there is evidence that alcohol suppresses pyramidal cells in the CA1 region of the hippocampus, cells which are important for forming memories of events. Alcohol suppresses them in a dose-dependent manner, similar to the BAC effect on blackouts in humans.

Another mechanism is interruption of long-term potentiation (LTP) in the hippocampus. After a group of hippocampal cells signals to other hippocampal cells, the subsequent signals induce a larger response, i.e. they are potentiated. The presence of alcohol can prevent this process occurring. Thus, while being intact before and after drinking, during an intoxication LTP is impaired. Alcohol is thought to mediate this blockade by interfering with the activation of the NMDA receptor, a key requirement for establishing LTP.

A third possible mechanism is that alcohol might induce its effects by impairing messages from structures that affect hippocampal functioning, such as the medial septum and the prefrontal cortex.^{8,10,11}

Trauma

Alcohol consumption can lead to confusion, ataxia and loss of social inhibition, and in some circumstances aggression, putting a person at risk of traumatic injury. This may take the form of injuries due to falls, fights or road traffic accidents.¹² Skull fractures and contusions may occur due to falls (Fig. 1). The latter are brought about by the brain

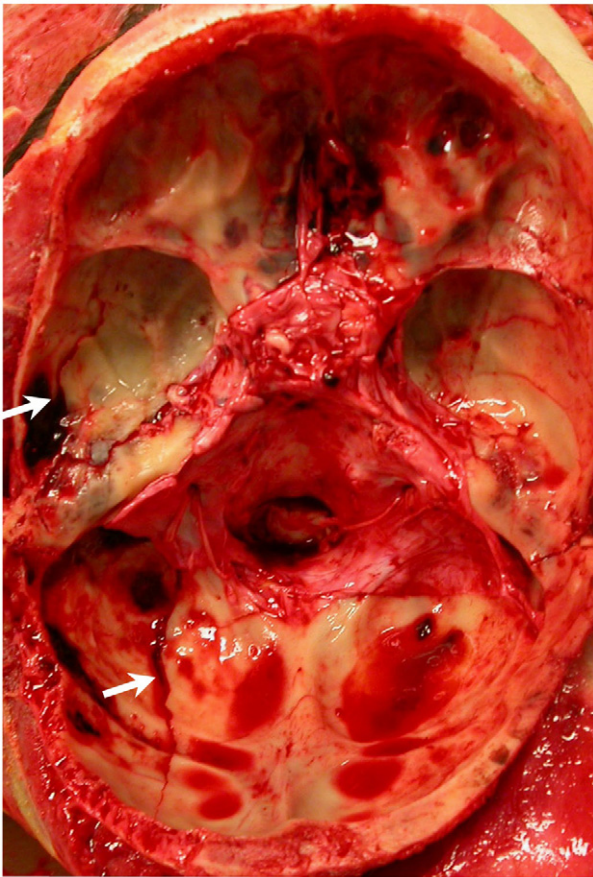


Figure 1 Skull fracture in the posterior and middle cranial fossae (arrows).

coming into contact with the bony protuberance of the skull and typically occur in the inferior and lateral aspects of the frontal pole and temporal pole (Figs. 2 and 3).¹² Falls are a leading risk factor for subdural haematomas (Fig. 4).¹² The process may be unilateral or bilateral and accumulates rapidly, causing coma. If bleeding is slower a chronic subdural haematoma develops, which may be accompanied by headache, confusion, unsteady gait or seizures. The haematoma may then resorb or may gradually enlarge, acting as a space-occupying mass.¹³ The presence of coagulopathy due to alcoholic liver disease contributes to this problem in some individuals. Dopaminergic dysfunction may play an important role in the pathophysiology of suicidal behaviour in patients with alcohol-related disorders.¹

Direct effects (chronic)

Withdrawal

Sudden cessation of alcohol consumption in heavy drinkers can precipitate tremors, irritability, anxiety, agitation, delirium tremens and seizures.¹⁴

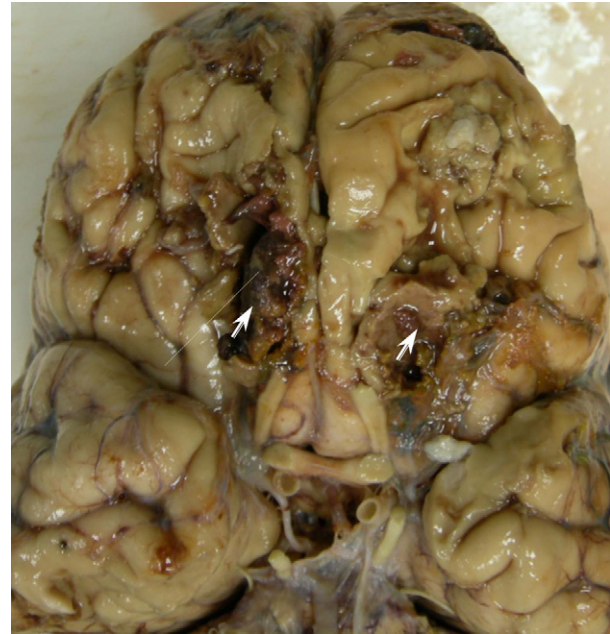


Figure 2 Brain viewed from the undersurface. Note the bilateral contusions in the inferior frontal lobes (arrows).

The severity of these symptoms increases with repeated withdrawal episodes, a phenomenon known as kindling. It is postulated that kindling may also contribute to a patient's relapse risk and to alcohol-related brain damage and cognitive impairment.¹⁵

Cerebral atrophy

From pathological and radiological (computed tomography (CT) and magnetic resonance imaging (MRI)) studies, cerebral atrophy, particularly involving the frontal cortex, has been documented in patients suffering from alcohol addiction. Atrophy can also occur in the hippocampus, corpus callosum, thalamus, mamillary bodies and cerebellar cortex. However, the changes in the diencephalon and mamillary bodies are associated with thiamine deficiency. Based on pathological examination, white matter loss is greater than grey matter loss, although the number of neurones in the frontal lobe is also decreased.^{16–18}

Radiological studies, i.e. CT, confirm this cerebral atrophy predominantly involving the frontal lobes.¹⁹ MRI studies suggest that the changes in the frontal lobes are at least partially reversible with abstinence, but return and progress with further drinking, the changes being related to reduced grey and white matter consistent with pathological observations. It has been suggested that older people and females are particularly susceptible, but this has yet to be confirmed.²⁰

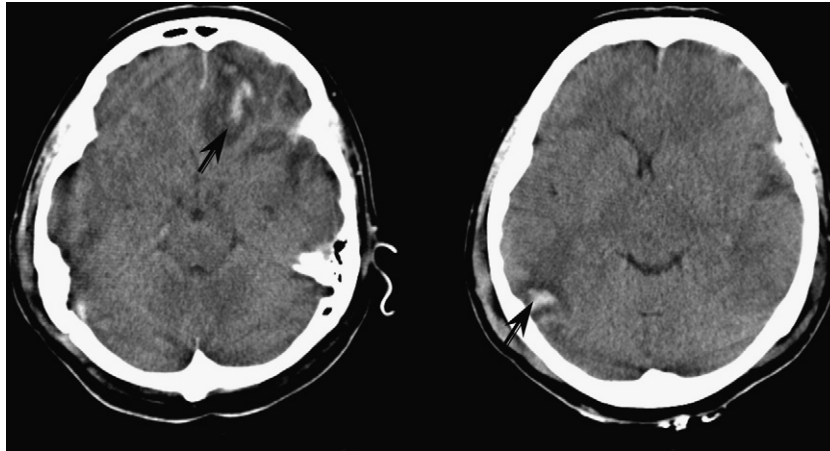


Figure 3 CT revealing a large left frontal contusion with an associated right parietal lobe contusion in the location of a contra-coup injury (arrows).



Figure 4 CT of an acute subdural haematoma over the left hemisphere with effacement of the sulci.

Newer imaging techniques, such as diffusion tensor imaging (DTI), have revealed abnormalities in the corpus callosum associated with reduced attention span and impaired working memory.²⁰ Positron emission tomography (PET) studies show hypometabolism in the frontal lobes bilaterally, especially the medial frontal lobes, which correlate with impaired performance on neurophysiological tests.^{17,21} Single photon emission CT (SPECT) studies of cerebral blood flow have shown global reduction in cerebral blood flow but more pronounced in the frontal lobes.²²

Dementia

Whether or not a subcategory of dementia purely related to alcohol consumption exists is a matter for debate. Whereas acute consumption, even in relatively small amounts, can impair memory leading to blackouts, chronic consumption with

thiamine deficiency can cause Wernicke–Korsakoff syndrome (WKS). It has yet to be proven that alcohol consumption can cause persistent memory impairment in the setting of adequate nutrition. Chronic alcohol consumption, however, can lead to detectable abnormalities in brain matter that are associated with impairment of perceptual and cognitive functions.¹⁷ People with moderate alcohol consumption seem to be spared these effects.²³ Furthermore, the Copenhagen City Heart Study and later longitudinal studies have shown a protective effect of mild-to-moderate alcohol consumption on the risk of developing dementia or cognitive impairment.^{2,3}

Cerebellar degeneration

The aetiology of cerebellar degeneration is multifactorial but advanced age, malnutrition and alcohol are important factors.^{16,24} Atrophy may be entirely asymptomatic or may give rise to ataxia affecting the lower limbs and trunk. The pathological correlate is shrinkage of the cerebellar folia and widening of the sulci, involving mainly the vermis. Histological examination shows loss of Purkinje, molecular and granular layer cells in the most severely affected areas.

Osmotic demyelination (central pontine and extrapontine myelinolysis)

Although initially described in the pons, osmotic demyelination may be extrapontine, and was originally described in 1959 in association with chronic alcoholism and malnutrition.²⁵ It occurs after rapid changes in plasma sodium concentrations from hypernatraemia, hyponatraemia or rapid correction of either. This is an acute condition that is frequently fatal: mild forms may be asymptomatic. Pathologically the pontine white matter,

including the middle cerebellar peduncle, is the most sensitive area. Histology reveals demyelination with preservation of neurons and axons, and absence of inflammation.

Marchiafava–Bignami disease

This rare complication of chronic alcoholism is characterized by lesions involving the corpus callosum with evidence of demyelination.²⁶ Clinically, patients have a long-standing history of excess alcohol consumption. They may present acutely with confusion, seizures, ataxia, dysarthria or coma which may be fatal. In the chronic stage, dementia and spastic paralysis occur. Other features such as aphasia, tremor or homonymous hemianopia have been described and may represent a disconnection syndrome.

Macroscopically, it is a necrotic cystic lesion involving the corpus callosum. Other areas of white matter may also be involved symmetrically. Microscopic examination reveals destruction of axons and myelin within the central necrotic cystic areas. In the periphery both axons and myelin are spared and there is usually fibrillary gliosis and lipid-filled macrophages. Relative sparing of the axons in the periphery in some parts of the lesion has been reported.^{16,26}

Marchiafava–Bignami disease is primarily regarded as a pathological diagnosis. However, advances in neuroimaging techniques allow the detection of the lesion during life.^{27,28}

Morel's laminar sclerosis

Morel's laminar sclerosis is an area of neuronal loss with astrocytic gliosis occurring in the third cortical layer of the frontal lobe in alcoholic patients. It has been suggested that this is a process secondary to Marchiafava–Bignami disease. Imaging studies have shown lesions in the lateral parts of the frontal lobe that are hyperintense on T2-weighted MRI, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) in patients with Marchiafava–Bignami disease. These lesions may well represent Morel laminar sclerosis. However, pathological confirmation has not yet been possible. Prolonged seizure activity and oedema are alternative explanations for the MRI appearances.^{16,28}

Hepatic encephalopathy and chronic hepatocerebral degeneration

Alcoholic liver disease may lead to a coagulopathy and contribute to intracranial haemorrhage and subsequent brain damage. It may also cause hepatic encephalopathy which in the acute form is characterized by confusion, psychosis, sleep

disturbances and attention deficits. Chronic hepatocerebral degeneration occurs after recovery from acute hepatic encephalopathy. The features are those of delirium with or without psychosis, ataxia, dysarthria, choreoathetosis and corticospinal tract signs. Thus, the features of this syndrome are broader than those found with alcoholic cerebellar degeneration.²⁹

Histology in hepatic encephalopathy shows pairs and triplets of astrocytes known as Alzheimer type II astrocytes. These may be found in the globus pallidus and cortex. Manganese and ammonia, both of which accumulate in hepatic encephalopathy, are felt to be important in the development of these changes.³⁰

Neuropathy and myopathy

Abusers of alcohol may develop compression neuropathies, involving the peroneal nerve from compression in the region of the neck of the fibula when lying, or radial nerve when the upper arm is placed on a backrest or bench.³¹ Myopathic features such as gait disturbances, cramps, local pain and reduced muscle mass may also occur. This myopathy is estimated to occur in up to 50% of alcohol abusers.³² It is characterized clinically by a reduction in muscle bulk of up to 30% and pathologically by type 2 fibre atrophy. It occurs independent of peripheral neuropathy, malnutrition and overt liver disease.³²

Indirect effects (nutritional)

Wernicke–Korsakoff syndrome (thiamine deficiency)

The spectrum of thiamine (vitamin B1) deficiency includes Wernicke's encephalopathy (WE) and Korsakoff psychosis (Korsakoff amnesic disorder or alcohol amnesic disorder). Due to the common pathogenic mechanism and the occurrence of features of both disorders in a given patient, WKS is commonly used to describe the CNS consequences of thiamine deficiency.³³ Clinically, the classical description of WE is a triad of confusion, ataxia and ophthalmoplegia. It is potentially reversible but can progress to Korsakoff amnesic disorder. Korsakoff amnesic disorder is usually described as an irreversible state of anterograde amnesia with severe impairment in forming new memories. This is commonly associated with confabulation and some element of retrograde amnesia. It is potentially fatal. Psychosis in the form of hallucinations, auditory or visual, and delusions may occur acutely and may persist.

These classical descriptions are clinically useful. However, in real life the distinction between pure WE and pure Korsakoff amnesic disorder is blurred and they should be viewed as different manifestations of the same entity. The spectrum of WKS also includes asymptomatic cases, possibly due to repeated subclinical episodes of WE.³⁴ It has been suggested that a subclinical deficiency of thiamine can cause working memory impairment.³⁵

Pathologically the mamillary bodies are symmetrically reduced in size. Involvement of structures outside the mamillary bodies seems to be associated with a worse prognosis and amnesia. Microscopic examination may reveal haemosiderin-laden macrophages, ballooned neurons and gliosis.³⁶

Imaging studies (MRI, FLAIR and DWI) show that lesions may be detectable in live patients. Symptomatic patients with WKS may still have normal scans. The presence of disease outside the mamillary bodies in the subacute phase correlates with a poor response to thiamine.^{37,38}

Thiamine deficiency plays a central role in WKS.³⁵ Thiamine is a co-factor for the assembly of some of the enzymes required for glucose metabolism and is not produced by humans. Therefore, dietary intake, transport to cellular sites of action and binding to enzymes are important. Patients who are addicted to alcohol consume a suboptimal amount of thiamine. Additionally alcohol impairs the transport of thiamine. From a clinical viewpoint it is important to be aware that a glucose load can exacerbate thiamine deficiency, be it from ethanol excess, malabsorptive states or other causes. Therefore, thiamine should be administered promptly to 'at-risk' patients receiving parenteral nutrition and replacement should continue after the acute illness until an adequate dietary intake is established.

Alcoholic pellagra (niacin deficiency)

Pellagra, the manifestations of nicotinic acid or niacin deficiency, may occur in patients who derive most of their nutrition from alcoholic beverages. Clinically, the manifestations are usually described as dermatitis, diarrhoea and dementia, although it is usually an acute confusional state more consistent with delirium than dementia. In a given patient some of these features may be absent and other features such as hypertonicity, myoclonus and psychosis may be present. The hypertonicity is extrapyramidal and described as oppositional hypertonus (gegenhalten).³⁹

Histology shows ballooned neurons in pyramidal Betz cells of the motor cortex, pontine nuclei, dorsal nucleus of the vagus, nucleus ambiguus, nuclei cuneatus and gracilis, trigeminal nerve nuclei, oculomotor nucleus and anterior motor

neurons of the spinal cord. WKS features and Marchiafava–Bignami disease can coexist in these patients.^{39,40}

Toxic polyneuropathy

This manifests clinically as pain, parasthesia and numbness in a glove and stocking distribution. Weakness and ultimately atrophy of peripheral muscles, most marked distally, loss of tendon reflexes and involvement of the autonomic nervous system may also occur. It results from inadequate nutrition, mainly deficiencies of thiamine and other B vitamins. Alcohol itself has a direct toxic effect.³¹

Toxic nutritional optic neuropathy ('tobacco alcohol amblyopia')

Alcohol-dependent people may develop subacute or chronic bilateral painless loss of visual acuity with poor colour vision and a central scotoma. Fundoscopy and peripheral visual fields may be normal. The underlying damage occurs at any part of the papillomacular bundle, i.e. the retina, optic nerve, optic chiasm, optic tract or the lateral geniculate nuclei. Microscopically, myelin and axonal loss is seen together with a gliotic response. The optic radiation and cortex are spared. Nutritional deficiency is thought to play a central role, with tobacco and, less likely, alcohol use being modifying factors. Some patients with this condition have been found to suffer from a mitochondrial disorder, i.e. Leber's hereditary optic neuropathy.^{16,41,42}

Conclusion

Ethanol has many direct and indirect effects on the nervous system. In moderation it can have beneficial effects. There appears to be no safe limit for alcohol consumption in pregnancy. In adults acute intoxication with sufficiently large quantities of alcohol can lead to cardiorespiratory depression and death. However, there is considerable variation in this response, as tolerance occurs with continuous exposure.

Practice points

- Alcohol may affect the developing nervous system
- Its effects on the developed nervous system may be acute or chronic, direct or indirect
- Not all people exposed to similar amounts of alcohol have the same outcome
- Genetic and nutritional factors may affect our ability to metabolize alcohol

References

1. Sher L. Alcohol and suicide: neurobiological and clinical aspects. *Sci World J* 2006;**6**:700–6.
2. Truelsen T, Thudium D, Gronbaek M. Amount and type of alcohol and risk of dementia: the Copenhagen City Heart Study. *Neurology* 2002;**59**:1313–9.
3. Ganguli M, Vander Bilt J, Saxton JA, Shen C, Dodge HH. Alcohol consumption and cognitive function in late life: a longitudinal community study. *Neurology* 2005;**65**:1210–7.
4. Centers for Disease Control and Prevention. Alcohol consumption among women who are pregnant or who might become pregnant united states, 2002. *MMWR* 2004;**53**:1178–81.
5. White AM, Swartzwelder HS. Age-related effects of alcohol on memory and memory-related brain functions in adolescents and adults. *Rec Dev Alcohol* 2005;**17**:161–76.
6. Kugelberg FC, Jones AW. Interpreting results of ethanol analysis in post mortem specimens: a review of the literature. *Forensic Sci Int* 2007;**165**:10–29.
7. Riley EP, McGee CL. Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior. *Exp Biol Med* 2005;**230**:357–65.
8. White A. What happened? Alcohol memory blackouts, and the brain. *Alcohol Res Health* 2003;**27**:186–96.
9. Knight JR, Palacios JN, Shannon M. Prevalence of alcohol problems among pediatric residents. *Arch Pediatr Adolesc Med* 1999;**153**:1181–3.
10. Wall PM, Messier C. The hippocampal formation—orbitomedial prefrontal cortex circuit in the attentional control of active memory. *Behav Brain Res* 2001;**127**:99–117.
11. Curtis CE, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. *Trends Cogn Sci* 2003;**7**:415–23.
12. Savola O, Niemelä O, Hillbom M. Alcohol intake and the pattern of trauma in young adults and working aged people admitted after trauma. *Alcohol Alcohol* 2005;**40**:269–73.
13. Adhiyaman V, Asghar M, Ganeshram KN, Bhowmick BK. Chronic subdural haematoma in the elderly. *Postgrad Med J* 2002;**78**:71–5.
14. Saitz R. Introduction to alcohol withdrawal. *Alcohol Health Res World* 1998;**22**:5–12.
15. Becker HC. Kindling in alcohol withdrawal. *Alcohol Health Res World* 1998;**22**:25–33.
16. Mancall E. Some unusual neurologic diseases complicating chronic alcoholism. *Am J Clin Nutr* 1961;**9**:404–13.
17. Moselhy HF, Georgiou G, Kahn A. Frontal lobe changes with alcoholism: a review of the literature. *Alcohol Alcohol* 2001;**36**:357–68.
18. Harper C, Kril JJ, Holloway RL. Brain shrinkage in chronic alcoholics: a pathologic study. *Br Med J* 1985;**290**:501–4.
19. Cala LA, Jones B, Mastaglia FL, Wiley B. Brain atrophy and withdrawal impairment in heavy drinkers—a clinical psychometric and tomography study. *Aust N Z J Med* 1978;**8**:147–53.
20. Rosenbloom M, Sullivan E, Pferrerbaum A. Using magnetic resonance imaging and diffusion tensor imaging to assess brain damage in alcoholics. *Alcohol Res Health* 2003;**27**:147–52.
21. Adams KM, Gilman S, Koeppe R, Kluin KJ. Correlation of neuropsychological function with cerebral metabolic rate in subdivisions of frontal lobes of older alcoholic patients measured with (sup-1-sup-8F) fluorodeoxyglucose and positron emission tomography. *Neuropsychology* 1995;**9**:275–80.
22. Gansler DA, Harris GJ, Oscar-Berman M, et al. Hypoperfusion of inferior frontal brain regions in abstinent alcoholics: a positron SPECT study. *J Stud Alcohol* 2000;**61**:32–7.
23. Kubota M, Nakazaki S, Hirai S, Saeki N, Yamaura A, Kusaka T. Alcohol consumption and frontal lobe shrinkage: study of 1432 non-alcoholic subjects. *J Neurol Neurosurg Psychiatr* 2001;**71**:104–6.
24. Nicolás JM, Fernández-Solá J, Robert J, et al. High ethanol intake and malnutrition in alcoholic cerebellar shrinkage. *QJM* 2000;**93**:449–56.
25. Adams RD, Victor M, Mancall EL. Central pontine myelinolysis. *Arch Neurol Psychiatr* 1959;**81**:159–72.
26. Koeppen A, Barron K. Marchiafava–Bignami disease. *Neurology* 1978;**28**:290–4.
27. Arbelaez A, Pajon A, Castillo M. Acute Marchiafava–Bignami disease: MR findings in two patients. *Am J Neuroradiol* 2003;**24**:1955–7.
28. Johkura K, Naito M, Naka T. Cortical involvement in Marchiafava–Bignami disease. *Am J Neuroradiol* 2005;**26**:670–3.
29. Greenberg D, Lee J, Lautenschlager N. Management and treatment of psychotic manifestations in older patients with alcoholism: Part II. *Clin Geriatrics* 2004;**12**:33–41.
30. Butterworth RF. Hepatic encephalopathy—a serious complication of alcoholic liver disease. *Alcohol Res Health* 2003;**27**:143–5.
31. Schuchardt V. Alcohol and the peripheral nervous system. *Ther Umsch* 2000;**57**:196–9.
32. Preedy VR, Ohlendieck K, Adachi J, et al. The importance of alcohol-induced muscle disease. *J Muscle Res Cell Motil* 2003;**24**:55–63.
33. Victor M, Yakovlev PI. S. S. Korsakoff's psychic disorder in conjunction with peripheral neuritis. A translation of Korsakoff's original article with brief comments on the author and his contribution to clinical medicine. *Neurology* 1955;**5**:394–406.
34. Harper C. The incidence of Wernicke's encephalopathy in Australia—a neuropathological study of 131 cases. *J Neurol Neurosurg Psychiatr* 1983;**46**:593–8.
35. Martin P, Singleton C, Hiller-Sturmhofel S. The role of thiamine deficiency in alcoholic brain disease. *Alcohol Res Health* 2003;**27**:134–41.
36. Freiesleben W, Söylemezoglu F, Lowe J, Janzer RC, Kleihues P. Wernicke's encephalopathy with ballooned neurons in the mamillary bodies: an immunohistochemical study. *Neuropathol Appl Neurobiol* 1997;**23**:36–42.
37. Weidauer S, Nichtweiss M, Lanfermann H, Zanella FE. Wernicke encephalopathy: MR findings and clinical presentation. *Eur Radiol* 2003;**13**:1001–9.
38. Antunez E, Estruch R, Cardenal C, Nicolas JM, Fernandez-Sola J, Urbano-Marquez A. Usefulness of CT and MR imaging in the diagnosis of acute Wernicke's encephalopathy. *Am J Roentgenol* 1998;**171**:1131–7.
39. Seradaru M, Hausser-Hauw C, Laplane D, et al. The clinical spectrum of alcoholic pellagra encephalopathy: a retrospective analysis of 22 cases studied pathologically. *Brain* 1987;**110**:301–14.
40. Park SH, Na DL, Lee JH, et al. Alcoholic pellagra encephalopathy combined with Wernicke disease. *J Korean Med Sci* 1991;**6**:87–93.
41. Cullom ME, Heher KL, Miller NR, Savino PJ, Johns DR. Leber's hereditary optic neuropathy masquerading as tobacco-alcohol amblyopia. *Arch Ophthalmol* 1993;**111**:1482–5.
42. Ordunez-Garcia PO, Nieto FJ, Espinosa-Brito AD, Caballero B. Cuban epidemic neuropathy, 1991 to 1994: history repeats itself a century after the "amblyopia of the blockade". *Am J Public Health* 1996;**86**:738–43.