Chapter 5
Central Nervous System Alterations in Alcohol Abuse

Andreas Büttner and Serge Weis

Contents

Abstract Alcohol abuse and dependence is a serious medical and economic problem in the Western countries as its effects on the central nervous system (CNS) are wide-ranging. The main factors contributing to alcohol-induced brain damage are associated with nutritional deficiencies and repeated withdrawal syndrome. CNS lesions associated with alcoholism include brain atrophy and central pontine myelinolysis. At least four distinct conditions leading to dementia, i.e. Wernicke-Korsakoff syndrome, hepatocerebral degeneration, Marchiafava-Bignami disease, and pellagrous encephalopathy, have a close association with chronic alcoholism, whereby the role of alcohol in their causation is secondary. A disproportionate loss of cerebral white matter relative to cerebral cortex suggests that a major neurotoxic effect of chronic alcohol consumption affects the white matter. Brain atrophy in alcoholics has been demonstrated in various studies. There is a regional selectivity, with the frontal lobes being particularly affected,

A. Büttner
Institute of Legal Medicine, University of Munich, Munich, Germany
e-mail: Andreas.Buettner@med.uni-muenchen.de

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which might explain the high incidence of cognitive dysfunction observed in alcoholics. In functional genomic studies reported so far, the identity and the number of dysregulated genes, the specific pathways involved and the direction of change show profound interstudy variations and, thus, remain inconclusive.

Keywords Alcohol · Central nervous system · Central pontine myelinolysis · Wernicke-Korsakoff syndrome · Neuropathology · Forensic pathology

5.1 Introduction

Alcohol abuse and dependence are serious medical and economic problems in the Western countries as the effects of alcohol on the central nervous system (CNS) are wide ranging. Direct toxicity of ethanol and its first metabolite acetaldehyde accounts for some of these effects by altering basic physiological and neurochemical functions [1], which ultimately result in structural damage. At the cellular level, alcohol affects brain function primarily by interfering with the action of glutamate, gamma amino butyric acid (GABA), and other neurotransmitters [2].

Similar to other drugs of abuse, the mesolimbic dopaminergic reward pathways are crucial for the reinforcing effects of alcohol and play a central role in alcohol addiction [3, 4, 5, 6, 7, 8, 9]. Recent knowledge of the neurobiological basis of alcoholism suggests that the pharmacological and behavioral effects of alcohol are mediated through its action on neuronal signal transduction pathways and ion channels, G-protein coupled receptors and other receptor systems [10, 11].

Sudden death in alcoholics is nearly equally distributed between trauma, natural causes, acute intoxication and alcohol-related diseases [12]. Upon forensic autopsy, brain abnormalities in alcoholics have been described to occur in up to 70% of the persons [13]. CNS lesions associated with alcoholism include brain atrophy and central pontine myelinolysis. Other frequent findings are myelopathy, neuropathy, subdural hematoma and/or cortical contusions and cerebrovascular lesions [13, 14]. Approximately 10% of alcoholics develop an organic mental disorder/severe cognitive impairments [15]. At least four distinct dementing conditions – Wernicke-Korsakoff syndrome, acquired hepatocerebral degeneration, Marchiafava-Bignami disease, and pellagrous encephalopathy – have a close association with chronic alcoholism; however, the role of alcohol in the causation is secondary [16]. Alcoholic dementia is said to consist of global severe amnesia and intellectual impairment [17, 18, 19]. However, the question whether there is a persistent dementia attributable to the direct toxic effects of alcohol on the brain is still unclear. This is mainly due to the fact that a primary alcoholic dementia lacks a distinctive, well-defined pathology. Therefore, its pathomechanisms must remain ambiguous until its morphologic bases are established [16].

Although a variety of neuropathological changes have been described in the brain of chronic alcoholics, it is difficult to elucidate the exact pathogenetic mechanisms causing the CNS damage since these persons often have concurrent damage to other organs, e.g., liver cirrhosis, repeated traumatic head injuries, malnutrition [20, 21]. The development of brain damage may further be complicated by polysubstance abuse [20]. Moreover, the type and severity of brain damage are influenced by several other factors, such as type and amount of alcoholic beverages, age of onset of drinking, lifetime alcohol consumption and genetic vulnerability [15, 22].

Thus, the neuropathological lesions encountered in chronic alcoholics are most probably the end result of a variety of etiological factors. Increasing evidence indicates that the main factors contributing to alcohol-induced brain damage are associated with nutritional deficiencies and repeated withdrawal syndrome [15]. These two factors may induce neurotoxicity by increased glutamatergic transmission and overactivation of NMDA receptor-induced excitotoxicity [15]. Nevertheless, it is now well established that even uncomplicated alcoholics, who have no specific neurological or hepatic problems, show signs of cognitive dysfunction and brain damage [23].

Some studies suggest that females are more vulnerable to alcohol-induced brain damage than males [24]; however, the evidence remains inconclusive [25, 26, 27].

5.2 Neuroimaging

Neuroradiological studies have demonstrated cerebral atrophy which has occasionally been accompanied by cognitive deficits and was at least partially reversible.

Computed tomography (CT) studies have shown significantly increased ventricular size [28] and cortical atrophy in alcoholics, predominantly of the frontal lobe [29, 30, 31, 32].

Magnetic resonance imaging (MRI) studies confirmed the CT findings in the manner that the frontal lobes are preferentially vulnerable to chronic alcohol abuse [33]. In addition, significant volume deficits have been detected in the anterior hippocampus, the fronto-parietal and temporal gray matter [34, 35] as well as in the brainstem [36], diencephalon, and the caudate nucleus [34]. In chronic alcoholism, smaller hippocampal volumes have been shown to be proportional to the reduction of the brain volume [37]. Quantitative MRI demonstrated that the characteristic memory deficit of Korsakoff's syndrome involves significant bilateral hippocampal volume deficits and diencephalic pathology [38]. The patterns of circuitry disruption identified through structural and functional MRI studies suggest a central role for degradation of fronto-cerebellar neuronal nodes and connecting circuitry affecting widespread brain regions and contributing to the cognitive and motor deficits in alcoholics [39].

Studies with positron emission tomography (PET) have shown a decreased cerebellar and frontal lobe glucose utilization in alcoholics, confirming the preferential involvement of these brain regions in alcohol abuse [40, 41, 42, 43, 44, 45, 46, 47].

Single photon emission computed tomography (SPECT) analyses demonstrated a significant reduction of regional cerebral blood flow (rCBF) in alcoholics as compared to controls [48, 49, 50, 51]. The rCBF ratio was mainly reduced in frontal lobes [50, 52] and the greatest flow reduction was seen in persons with liver cirrhosis [53].

By using proton magnetic resonance spectroscopy (MRS), a reduced *N*-acetylaspartate (NAA)/choline and NAA/total creatine ratio as compared to age-matched controls has been described. As stated by the authors, the reduction in NAA is consistent with neuronal loss, whereas the reduction in choline suggests significant changes in the membrane lipids of alcoholics [36, 54].

Using magnetic resonance diffusion tensor imaging (MRDTI) to quantify the microstructure of brain tissue, alcoholics showed widespread white matter deficits, which are in contrast to the highly region-specific deficits seen in nutritional deficiency syndromes that can accompany alcoholism [55, 56].

5.3 Acute Intoxication

In acute alcohol intoxication there are no characteristic CNS alterations. Brain edema and vascular congestion (Fig. 5.1) are frequently seen, sometimes in conjunction with focal subarachnoid hemorrhage [57].

5.4 Brain Atrophy

Although the frequency and severity of cerebral atrophy in alcoholics is controversial, several autopsy studies have shown a reduction in brain weight and volume [14, 21, 58, 59]. The greatest reduction in brain weight was seen in

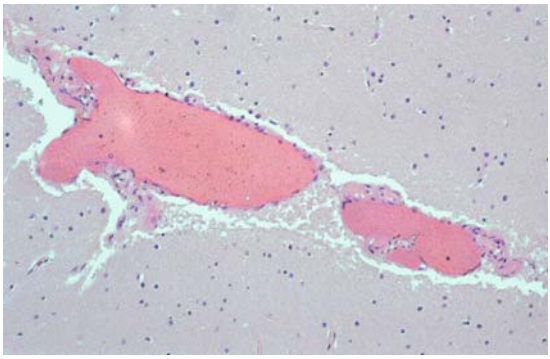

Fig. 5.1 Vascular congestion in acute alcohol intoxication (hematoxylin and eosin, magnification 100×)

alcoholics with additional complications, such as nutritional deficiencies or liver damage [58, 60]. Several studies demonstrated that this brain atrophy, often referred to as "brain shrinkage", is not due to a loss of gray matter but rather due to a reduction in the volume of the white matter [61, 62, 63]. The disproportionate loss of cerebral white matter relative to cerebral cortex suggests that a major neurotoxic effect of chronic alcohol consumption affects the white matter [61, 62, 63]. It has been suggested that the loss of white matter could be caused by changes in hydration [64]. However, postmortem studies could not support this hypothesis [65]. An alcohol-induced degeneration of myelinated fibres in the white matter could not be demonstrated [66]. Interestingly, these abnormalities may be reversed by abstinence from alcohol [21, 58, 59, 67, 68, 69].

In addition to the white matter changes, chronic alcohol consumption is associated with selective neuronal vulnerability, with the frontal lobes more seriously affected than other cortical regions [62, 70, 71]. Within the frontal cortex, this neurodegenerative process was confined to the superior frontal association cortex [60, 62, 63] affecting the non-GABAergic pyramidal neurons [63].

Recent studies have confirmed that the frontal lobe is especially vulnerable to alcohol-related brain damage (Fig. 5.2), whereby shrinkage in this area is largely due to a loss of white matter [71]. Moreover, disruption of fronto-cerebellar circuitry and function has been shown in alcoholism [72]. Since the frontal lobes have extensive connections to different cortical and subcortical areas of the brain, widespread alterations in brain functions result [71]. This might explain the high incidence of cognitive dysfunction observed in alcoholics who often develop frontal lobe symptoms with personality and behavioural changes, disinhibition, social and personal neglect, lack of insight, empathy and emotional control [73]. Such symptoms often increase the risk of engagement in and exposure to acts of violence carrying a risk of physical damage including head trauma and violent death [73].

Neuronal loss has been further shown to occur in the diencephalon, especially in patients with Wernicke-Korsakoff syndrome, and in the cerebellum [57, 59, 60,

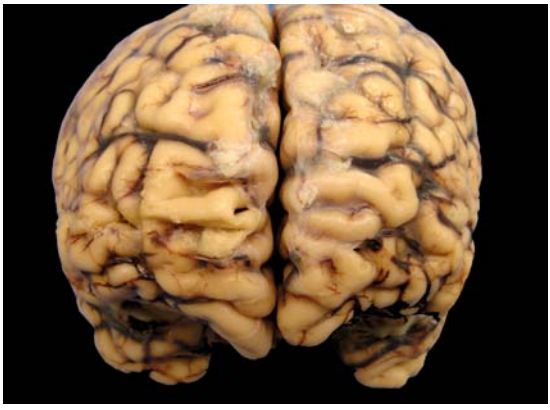

Fig. 5.2 Frontal lobe atrophy in long-term alcohol abuse

74, 75, 76, 77, 78, 79]. It is estimated that almost one half of all severe alcoholics have atrophy of the superior cerebellar vermis, which is clinically characterized by ataxia and incoordination of the lower limbs [79]. Besides a significant loss of Purkinje cells, the cerebellar molecular layer appears to be another vulnerable region in chronic alcoholics [80]. Microscopically, there is also proliferation of Bergmann glia in these cases. However, other groups found no consistent changes in the number of Purkinje cells or the structural volume for any cerebellar region in chronic alcoholics without Wernicke's encephalopathy, thus suggesting that chronic alcohol consumption per se does not necessarily damage the cerebellum [81, 82]. On the other hand, in alcoholics with Wernicke's encephalopathy, there is a significant decrease in Purkinje cell density in the flocculus and vermis as well as decreased volume of the molecular layer of the cerebellar vermis, indicating impairment of spino-cerebellar pathways [82].

The data on neuronal loss in the hippocampus of chronic alcoholics is contradictory. Some authors demonstrated an early neuronal loss [83], whereas others could not find a significant neuronal loss in any subregion of the hippocampus, despite a marked reduction in hippocampal volume which occurred exclusively in the white matter [84, 85].

No significant change was reported for the temporal [63, 70] or motor cortex [63], the basal ganglia [58], nucleus basalis of Meynert, or in the serotonergic raphe nuclei [21, 86]. Within the brainstem, a reduction in the number of serotonergic neurons was described in chronic alcoholics [87], while the number of pigmented cells in the locus coeruleus was unchanged [88].

A significant reduction of the corpus callosum has been detected in older alcoholics compared to age-matched controls [89, 90, 91]. This callosal thinning was even present in chronic alcoholics without clinical symptoms of severe liver disease, amnesia, or alcoholic dementia. The degree of this atrophy seems to correlate with the severity of alcohol intake [89].

In summary, brain atrophy in alcoholics has been demonstrated in various studies. There is a regional selectivity with the frontal lobes being particularly affected. However, the magnitude and topography of the atrophy, and the contributory factors are still not fully resolved [92]. The pathogenetic mechanisms leading to the selected vulnerability of specific brain regions to alcoholism is unknown. It is suggested that differences in the density of glutamatergic innervation or in subunit composition of glutamate receptors among different brain structures may contribute to this selectivity [93].

5.5 Glial Changes

In alcoholics, the morphology of astrocytes is markedly changed by exhibiting enlargement of their cell bodies and beading of the cellular processes [94]. In addition, GFAP-positive astrocytes were seen within and surrounding clusters of magnocellular neurons in the basal forebrain and hypothalamus. A patchy

loss of GFAP immunostaining was seen in most severe cases which could not be exclusively related to alcoholics with liver pathology [94].

A statistically significant loss of glial cells was found globally in the hippocampus of alcoholics compared with controls. A reduction of astrocytes and oligodendrocytes and, to a lesser degree, microglial cells accounted for this loss [85].

In animal models and human cell cultures it has been shown that chronic ethanol treatment stimulates astrocytes, upregulating the production and the expression of inflammatory mediators in the brain, and activating signalling pathways and transcription factors [95, 96, 97]. Furthermore, alcohol treatment increased cytochrome P4502E1 and induced oxidative stress in astrocytes [98] which might cause neurotoxicity. In addition, emerging data indicate that alcohol affects microglial cell development and function [96].

5.6 Dendritic and Synaptic Changes

Dendritic and synaptic alterations have been documented in alcoholics and these, together with receptor and neurotransmitter changes, may explain functional changes and cognitive deficits that precede the structural neuronal changes [21]. In "heavy drinkers", synaptic loss has been found in the superior layers of frontal Brodmann area 10, which was not related to liver disease [73].

5.7 Central Pontine Myelinolysis

Central pontine myelinolysis (CPM) is a demyelinating disease of the central portion of the base of the pons (Fig. 5.3A,B) often associated with demyelination of other brain areas [99, 100, 101, 102, 103]. The first cases were described in patients with a history of long-standing alcohol abuse and malnutrition [104],

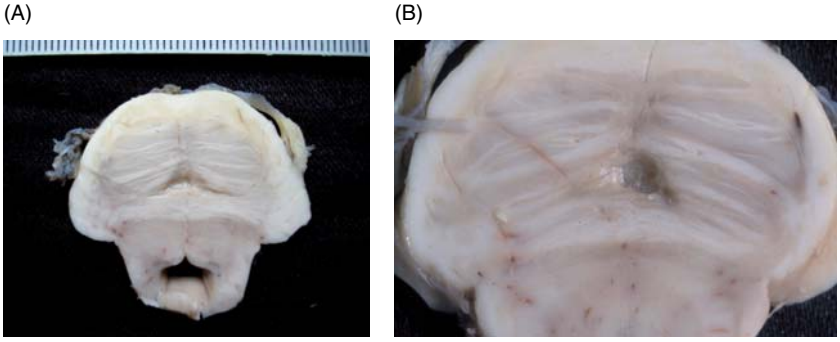

Fig. 5.3A,B Central pontine myelinolysis: destructive lesions in the pons

and chronic alcoholism is still a frequent underlying condition of persons with CPM [105]. However, in subsequent reports, CPM has been shown to occur most frequently in association with rapid correction of hyponatremia [100, 101, 102, 103, 106, 107, 108]. Especially alcoholism and liver diseases make patients more susceptible to the development of CPM.

Other causes include transplant patients, with the development of CPM being attributed to immunosuppressive agents [101, 105, 107, 109] and HIV-1 infection [110].

Depending on the involvement of other CNS structures, the clinical picture can vary considerably. CPM is most often an asymptomatic disorder with small, midline pontine lesions [102]. Destructive lesions in the corticospinal and the corticobulbar tracts in the pons lead to pseudobulbar paralysis with dysphagia, dysarthria, weakness of the tongue, and emotional lability. A large central pontine lesion can cause a locked-in syndrome depriving the patient of speech and the capacity to respond in any way except by vertical gaze and blinking [111]. Lesions involving the descending oculosympathetic tracts can cause bilateral miosis, whereas lesions that involve the lower pons can cause palsy of the sixth cranial nerve [102, 111]. In addition to lesions in the pons, other areas in the CNS can be affected. Such lesions are collectively referred to as extrapontine myelinolysis (EPM) and occur, in order of frequency, in the cerebellum, lateral geniculate body, thalamus, putamen, and cerebral cortex [100, 103, 105, 107]. CPM and EPM are summarized by the term osmotic demyelination disorders [105].

The outcome varies widely, from almost complete recovery to little or no improvement and subsequent death [105, 111, 112]. Since unexplained deaths may occur [113], therefore, a thorough examination of the pons must be performed at autopsy. On neuropathological examination, CPM usually presents as a single large symmetric focus of demyelination in the central part of the base of the pons, with sparing of axis cylinders (Fig. 5.4). No inflammatory changes are seen within the lesion and the blood vessels are unaffected [99, 100, 102, 103, 113, 114]. The etiology and pathogenesis of the myelin loss is still unclear [115].

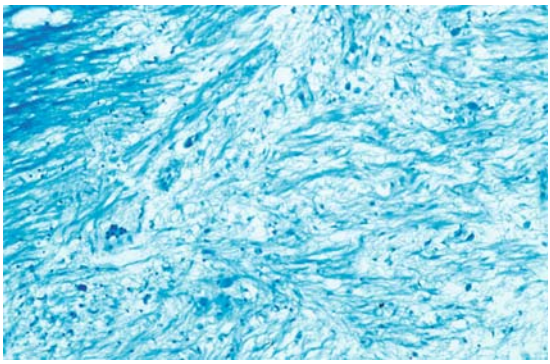

Fig. 5.4 Central pontine myelinolysis: marked demyelination (Luxol Fast Blue, magnification 100×)

5.8 Wernicke-Korsakoff Syndrome

The Wernicke-Korsakoff syndrome (WKS) is one of the most frequently seen neurological disorders associated with long-term and heavy alcohol abuse [15, 116, 117, 118]. Wernicke's encephalopathy is the acute phase of this syndrome and includes mental confusion, ophthalmoplegia (or nystagmus), ataxia, and loss of recent memory [117, 118, 119]. Despite abstinence and the administration of high dose of thiamine, about 25% of the affected persons develop severe memory disorders, the Korsakoff's syndrome which is mainly characterized by memory loss, learning deficits and confabulation [117, 118, 119, 120]. Korsakoff's psychosis is most likely the end-stage resulting from repeated episodes of Wernicke's encephalopathy.

The etiology is a deficiency of vitamin B1 (thiamine), a cofactor of several enzymes implicated in the glucose metabolism, rather than a direct toxic effect of alcohol [120, 121, 122]. The symptoms may be seen in either the acute or the long-term course of alcohol abuse [120]. The WKS can also occur in other conditions associated with vitamin B1 deficiency, e.g., gastrointestinal tract diseases, cerebrovascular disorders, or head trauma [116, 121]. Although the exact pathogenesis of the lesions is not completely understood, the association of vitamin B1 deficiency with intracellular and extracellular edema by glutamate(*N*-methyl-D-aspartate) receptor-mediated excitotoxicity seems to be an important mechanism [122].

Both conditions appear to have an identical neuropathology characterized by hemorrhages and other lesions around the ventricular system (Figs. 5.5 and 5.6) [117, 122, 123]. The principal structures affected are the mamillary bodies (Fig. 5.6), the walls of the third ventricle, the thalamus, the periaqueductal region of the midbrain and the floor of the fourth ventricle (Fig. 5.7) [116, 117, 122, 124]. The distribution and severity of the CNS lesions varies with the stages of the disease, which are generally considered to be acute, subacute or chronic [124].

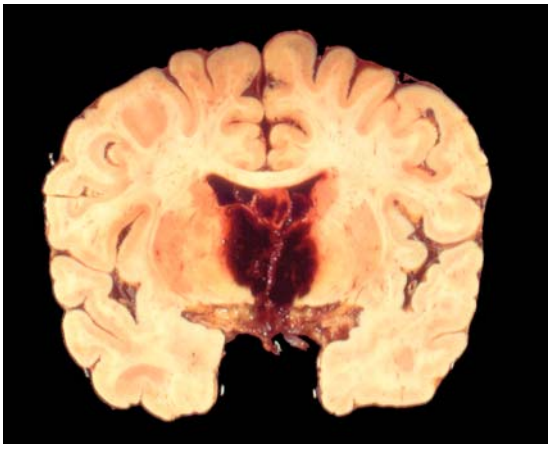

Fig. 5.5 Wernicke encephalopathy: widespread symmetrical hemorrhages around the ventricular system

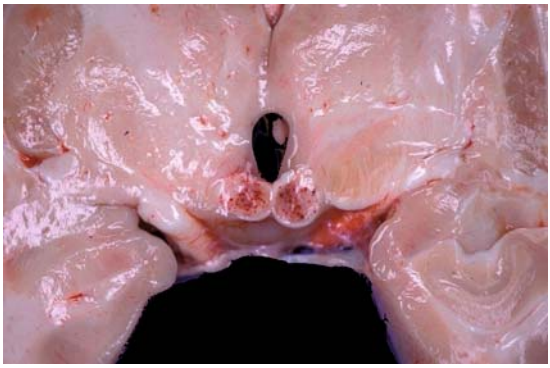

Fig. 5.6 Wernicke encephalopathy: symmetrical hemorrhages in the mammillary bodies

Subjects with acute and subacute disease seem to have more extensive and severe lesions than the chronic ones [122]. Microscopic changes can be related to the duration of the disease [123, 124]. The earliest alterations consist of rarefication of the neuropil by edema formation and petechial hemorrhages. In some instances these extend into the parenchyma to form "ball-like" microhemorrhages. Within 1–2 days there is endothelial hypertrophy and proliferation, which are maximal at about day 7–10. Tissue necrosis is occasionally seen but is more common in the thalamic nuclei. Neurons are relatively spared with the exception of the

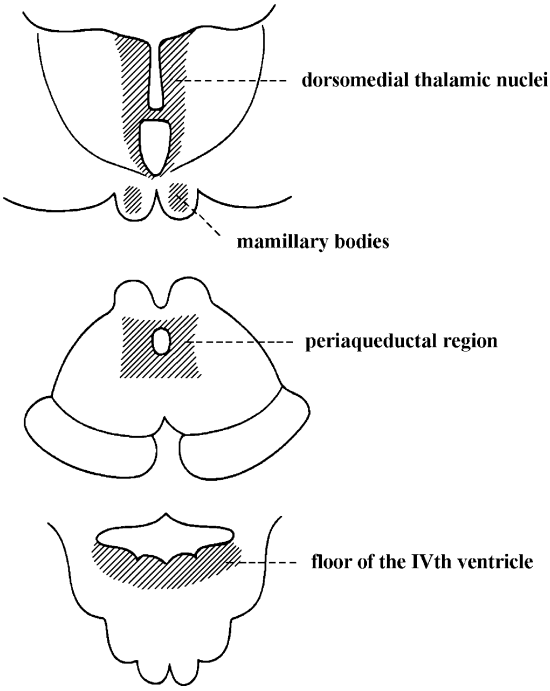

Fig. 5.7 Schematic drawing of the principal structures affected in Wernicke-Korsakoff syndrome

thalamic and olivary neurons. By the third or fourth day, there is an astrocytic reaction with increased numbers of nuclei and eosinophilic cytoplasm. Myelin and axons are often destroyed. There is usually no inflammatory reaction. In contrast to the lesion seen in the mamillary bodies, there is a massive loss of neurons with sparing of the neuropil, and only mild endothelial swelling within the thalamus [122, 123, 124].

The most consistent macroscopic finding in chronic WKS is shrinkage and brown discoloration of the mamillary bodies which varies from barely visible to subtotal destruction of the tissue [122, 123, 124]. Microscopically, there is a loss of myelin and axons, an astrogliosis and an apparent increase in vascularity in the shrunken mamillary bodies, but a relative preservation of neurons. Hemosiderin-laden macrophages are frequently seen and represent the residues of microhemorrhages (Fig. 5.8). Changes in other hypothalamic nuclei display a similar pattern but the changes are usually much less severe [122, 123, 124].

In the majority of chronic cases, the lesions are restricted to the mamillary bodies and the thalamus. Similar to the alterations within the mamillary bodies, the lesions in the thalamus vary from slight astrogliosis in the dorsomedial nucleus to extensive nerve cell loss in several of its nuclei [122, 123, 124]. While patients with Wernicke's encephalopathy often show neuronal loss in the dorsomedial nucleus of the thalamus, only patients with Korsakoff's psychosis seem to have cell loss in the medial [117] as well as in the anterior thalamic nuclei [125]. Furthermore, in both patient groups, a profound loss of serotonin- and acetylcholine-containing neurons has been found [117]. These observations suggest that cumulative lesions contribute to the amnesia seen in alcoholics with WKS, including deficits in serotonergic, cholinergic, and thalamic pathways.

Despite these apparent lesions, the exact morphological basis of this disorder is still controversial. Autopsy and MRI studies of alcoholic patients with WKS demonstrated gliotic lesions of the mamillary bodies; however, lesions of the mamillary bodies were often present in the absence of the amnestic syndrome [122, 126, 127]. It seems that the thalamus appears to be particularly susceptible to

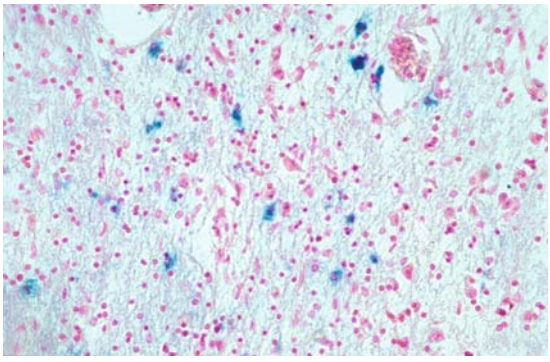

Fig. 5.8 Wernicke encephalopathy: hemosiderin-laden macrophages in the mammillary bodies representing residues of microhemorrhages (Iron stain, magnification 200×)

damage in WKS [122, 128]. Subsequent studies demonstrated that lesions of the mediodorsal nucleus of the thalamus correlated with the amnestic syndrome [118, 119, 122, 127] and the role of the mamillary bodies in this memory disorder was largely, although not entirely, dispelled [128].

Autopsy studies have shown that up to 80% of patients with the WKS were not diagnosed as such during life [129, 130, 131, 132, 133, 134]. Therefore, in cases with coma of unidentified cause or patients found dead who might have been alcoholics, a thorough neuropathologic examination is of utmost importance.

5.9 Hepatic Encephalopathy

Hepatic encephalopathy may arise as a complication of liver disease in alcoholics, particularly in the course of liver cirrhosis, which results in cognitive, psychiatric, and motor impairments [135, 136, 137]. The damaged liver can no longer clear neurotoxic substances from the blood which subsequently enter the brain and damage neurons and astrocytes. The clinical picture consists of a deterioration in the level of consciousness accompanied by decreased (or occasionally increased) psychomotor activity that, if left untreated, progresses to increasing drowsiness, stupor and eventual coma [135, 136, 137]. As the encephalopathy progresses, signs of pyramidal tract dysfunction such as hypertonia, hyperreflexia are common, eventually being replaced by hypotonia as coma develops. Treatment is largely supportive. The prognosis of patients who develop hepatic encephalopathy is poor. Following the first episode of overt hepatic encephalopathy, the 1-year survival is about 40%, falling to about 15% after 3 years [136]. The major causes of death in hepatic encephalopathy are brain edema and intracranial hypertension [138].

Although the pathogenesis of hepatic encephalopathy is not fully understood, there is considerable evidence that an ammonia-induced dysfunction of astrocytes is the major contributory factor [136, 139, 140]. Deficits in the uptake of glutamate by astrocytes from the extracellular space may lead to abnormal glutamatergic and GABAergic-mediated neurotransmission and subsequent neuronal excitotoxicity [139, 141]. In addition, an altered blood-brain barrier permeability [141, 142] and a combined derangement of cellular osmolarity coupled with cerebral hyperemia [138] appear to be involved in the generation of the edema.

In fulminant hepatic failure where hepatic encephalopathy develops within 8 weeks of the onset of liver disease, autopsy reveals brain edema and astrocyte swelling [139, 142]. In patients with liver cirrhosis and portal-systemic shunts, the typical finding is the Alzheimer type II astrocyte, which is the pathological hallmark of hepatic encephalopathy [140]. These cells show a characteristic swollen shape with a large, pale nucleus, prominent nucleolus and margination of chromatin, and are found in widespread regions of the brain including the

cortex and the lenticular, lateral thalamic, dentate and red nuclei [140, 141]. The majority of these cells show prominent immunoreactivity for S100P but not for GFAP, especially in the grey matter [143, 144]. Thus, this glial reaction with a rather selective deficit of GFAP metabolism has been termed "gliofibrillary dystrophy" [143].

5.10 Marchiafava-Bignami Syndrome

Marchiafava-Bignami disease is an extremely rare, severe and usually fatal neurological disorder associated with chronic alcoholism [145]. It is characterized by primary demyelination/necrosis and subsequent atrophy of the corpus callosum [124, 145, 146]. However, this lesion is not only limited to the corpus callosum but also affects the cortico-cortical and cortico-subcortical projections due to disconnection, and causes frontal lobe syndromes and dementia [145, 146].

Macroscopically, necrotizing, often cystic lesions of the corpus callosum are seen. Microscopically, there is prominent demyelination with relative sparing of the axons. Oligodendrocytes are reduced in number and there are numerous lipid-laden macrophages. Astrocytes show only mild reactive changes, but are more prominent in and around necrotizing lesions. Blood vessels often show proliferation and hyalinization of their walls [124, 146].

5.11 Pellagra Encephalopathy

Nicotinamide deficiency may result in a rare condition, alcoholic pellagra encephalopathy, which often has a similar clinical presentation to Wernicke-Korsakoff syndrome which includes confusion and/or clouding of consciousness, marked oppositional hypertonus and myoclonus [147, 148]. On neuropathological examination, no gross macroscopic changes are usually visible. Microscopically, the major finding is a central chromatolysis of neurons, predominantly in the brainstem and in the cerebellar dentate nuclei. The affected neurons are ballooned with a loss of Nissl substance and eccentrically located nuclei. Nuclei of cranial nerves, the reticular nuclei, arcuate nuclei and posterior horn cells, may also be involved. Glial cells, myelin or blood vessels are not affected [149, 150].

5.12 Stroke

Recent heavy alcohol intake seems to be an independent risk factor for all major subtypes of stroke [151] and to be associated with cerebral infarcts localized in the putamen and superior anterior cerebral artery area [152]. The ultimate mechanisms leading to this increased risk are unclear [151].

Concerning the relation between moderate alcohol consumption and the risk of stroke, there is insufficient epidemiologic evidence to conclude whether recent alcohol use affects the risk of either ischemic or hemorrhagic stroke [153]. Both occasional ethanol intoxication and regular heavy drinking seem to carry an increased risk of subarachnoid hemorrhage [154].

5.13 Functional Genomic Alterations

Although functional genomic studies have failed to identify a single alcoholism gene, they have demonstrated important pathways and gene products that may contribute to the risk of alcohol abuse and alcoholism [155, 156, 157, 158]. Several research groups have searched for alcohol-responsive genes using microarrays. It could be shown that the alteration in expression of genes involved in DNA repair, myelination, signal transduction, ubiquitination as well as proteasome-related genes represent common changes seen in the various studies performed in alcohol abusers. However, the identity and number of dysregulated genes reported so far, the specific pathways involved, and the direction of change differs profoundly between the reports and thus remains inconclusive [11, 158].

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References

1. Zimatkin SM, Deitrich RA (1997) Ethanol metabolism in the brain. Addiction Biol 2:387–399
2. Oscar-Berman M, Shagrin B, Evert DL, Epstein C (1997) Impairments of brain and behavior: the neurological effects of alcohol. Alcohol Health Res World 21:65–75
3. Appel SB, McBride WJ, Diana M, Diamond I, Bonci A, Brodie MS (2004) Ethanol effects on dopaminergic "reward" neurons in the ventral tegmental area and the mesolimbic pathway. Alcohol Clin Exp Res 28:1768–1778
4. Boileau I, Assaad J-M, Pihl RO, Benkelfat C, Leyton M, Diksic M et al. (2003) Alcohol promotes dopamine release in the human nucleus accumbens. Synapse 49:226–231
5. Diana M, Brodie M, Muntoni A, Puddu MC, Pillolla G, Steffensen S et al. (2003) Enduring effects of chronic ethanol in the CNS: basis for alcoholism. Alcohol Clin Exp Res 27:354–361
6. Herz A (1997) Endogenous opioid systems and alcohol addiction. Psychopharmacology 129:99–111
7. Lê AD, Kiianmaa K, Cunningham CL, Engel JA, Ericson M, Soderpalm B et al. (2001) Neurobiological processes in alcohol addiction. Alcohol Clin Exp Res 25: 144S–151S
8. Noble EP (1996) Alcoholism and the dopaminergic system: a review. Addict Biol 1:333–348
9. Tupala E, Tiihonen J (2004) Dopamine and alcoholism: neurobiological basis of ethanol abuse. Prog Neuropsychopharmacol Biol Psychiatry 28:1221–1247

10. Basavarajappa BS, Hungund BL (2005) Role of the endocannabinoid system in the development of tolerance to alcohol. Alcohol Alcohol 40:15–24
11. Flatscher-Bader T, van der Brug MP, Landis N, Hwang JW, Harrison E, Wilce PA (2006) Comparative gene expression in brain regions of human alcoholics. Genes Brain Behav 5(Suppl 1):78–84
12. Clark JC (1988) Sudden death in the chronic alcoholic. Forensic Sci Int 36:105–111
13. Skullerud K, Andersen SN, Lundevall J (1991) Cerebral lesions and causes of death in male alcoholics. A forensic autopsy study. Int J Legal Med 104:209–213
14. Torvik A (1987) Brain lesions in alcoholics: neuropathological observations. Acta Med Scand Suppl 717:47–54
15. Fadda F, Rossetti ZL (1998) Chronic ethanol consumption: from neuroadaptation to neurodegeneration. Prog Neurobiol 56:385–431
16. Victor M (1994) Alcoholic dementia. Can J Neurol Sci 21:88–99
17. Cutting J (1978) The relationship between Korsakoff's syndrome and "alcoholic dementia". Br J Psychiat 132:240–251
18. Martin PR, Adinoff B, Weingartner H, Mukherjee AB, Eckardt MJ (1986) Alcoholic organic brain disease: nosology and pathophysiologic mechanisms. Prog Neuropsychopharmacol Biol Psychiatry 10:147–164
19. Willenbring ML (1988) Organic mental disorders associated with heavy drinking and alcohol dependence. Clin Geriatr Med 4:869–887
20. Butterworth RF (1995) Pathophysiology of alcoholic brain damage: synergistic effects of ethanol, thiamine deficiency and alcoholic liver disease. Metab Brain Dis 10:1–8
21. Harper C (1998) The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? J Neuropathol Exp Neurol 57:101–110
22. Harper C, Dixon G, Sheedy D, Garrick T (2003) Neuropathological alterations in alcoholic brains. Studies arising from the New South Wales Tissue Resource Centre. Prog Neuropsychopharmacol Biol Psychiatry 27:951–961
23. Harper C, Matsumoto I (2005) Ethanol and brain damage. Curr Opin Pharmacol 5:73–78
24. Wuethrich B (2001) Does alcohol damage female brains more? Science 291:2077–2079
25. Harper CG, Smith NA, Kril JJ (1990) The effects of alcohol on the female brain – a neuropathological study. Alcohol Alcohol 25:445–448
26. Hommer DW (2003) Male and female sensitivity to alcohol-induced brain damage. Alcohol Res Health 27:181–185
27. Rosenbloom M, Sullivan EV, Pfefferbaum A (2003) Using magnetic resonance imaging and diffusion tensor imaging to assess brain damage in alcoholics. Alcohol Res Health 27:146–152
28. Fox JH, Ramsey RG, Huckman MS, Broske AE (1976) Cerebral ventricular enlargement. Chronic alcoholics examined by computerized tomography. JAMA 236:365–368
29. Carlen PL, Wortzman G, Holgate RC, Wilkinson DA, Rankin JG (1978) Reversible cerebral atrophy in recently abstinent chronic alcoholics measured by computed tomographic scans. Science 200:1076–1078
30. Ron MA (1977) Brain damage in chronic alcoholism: a neuropathological, neuroradiological and psychological review. Psychol Med 7:103–112
31. Rosse RB, Riggs RL, Dietrich AM, Schwartz BL, Deutsch SI (1997) Frontal cortical atrophy and negative symptoms in patients with chronic alcohol dependence. J Neuropsychiatry Clin Neurosci 9:280–282
32. Wilkinson DA (1982) Examination of alcoholics by computed tomographic (CT) scans. A critical reviews. Alcohol Clin Exp Res 6:31–45
33. Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO (1997) Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. Alcohol Clin Exp Res 21:521–529

34. Jernigan TL, Butters N, DiTraglia G, Schafer K, Smith T, Irwin M et al. (1991) Reduced cerebral grey matter observed in alcoholics using magnetic resonance imaging. Alcohol Clin Exp Res 15:418–427
35. Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A (1996) Relationship between alcohol withdrawal seizures and temporal lobe white matter volume deficits. Alcohol Clin Exp Res 20:348–354
36. Bloomer CW, Langleben DD, Meyerhoff DJ (2004) Magnetic resonance detects brainstem changes in chronic, active heavy drinkers. Psychiatr Res 132:209–218
37. Agartz I, Momenan R, Rawlings RR, Kerich MJ, Hommer DW (1999) Hippocampal volume in patients with alcohol dependence. Arch Gen Psychiatry 56:356–363
38. Sullivan EV, Marsh L (2003) Hippocampal volume deficits in alcoholic Korsakoff's syndrome. Neurology 61:1716–1719
39. Sullivan EV, Pfefferbaum A (2005) Neurocircuitry in alcoholism: a substrate of disruption and repair. Psychopharmacology (Berlin) 180:583–594
40. Adams KM, Gilman S, Koeppe RA, Kluin KJ, Brunberg JA, Dede D et al. (1993) Neuropsychological deficits are correlated with frontal hypometabolism in positron emission tomography studies of older alcoholic patients. Alcohol Clin Exp Res 17:205–210
41. Dao-Castellana MH, Samson Y, Legault F, Martinot JL, Aubin HJ, Crouzel C et al. (1998) Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings. Psychol Med 28:1039–1048
42. Gilman S, Koeppe RA, Adams K, Johnson-Greene D, Junck L, Kluin KJ et al. (1996) Positron emission tomographic studies of cerebral benzodiazepine-receptor binding in chronic alcoholics. Ann Neurol 40:163–171
43. Gilman S, Adams K, Koeppe RA, Berent S, Kluin KJ, Modell JG et al. (1990) Cerebellar and frontal hypometabolism in alcoholic cerebellar degeneration studied with position emission tomography. Ann Neurol 28:775–785
44. Sachs H, Russell JA, Christman DR, Cook B (1987) Alteration of regional cerebral glucose metabolic rate in non-Korsakoff chronic alcoholism. Arch Neurol 44:1242–1251
45. Samson Y, Baron JC, Feline A, Bories J, Crouzel C (1986) Local cerebral glucose utilisation in chronic alcoholics: a positron tomographic study. J Neurol Neurosurg Psychiatr 49:1165–1170
46. Volkow ND, Wang GJ, Hitzemann R, Fowler JS, Wolf AP, Pappas N et al. (1993) Decreased cerebral response to inhibitory neurotransmission in alcoholics. Am J Psychiatr 150:417–422
47. Wik G, Borg S, Sjogren I, Wiesel FA, Blomqvist G, Borg J et al. (1988) PET determination of regional cerebral glucose metabolism in alcohol-dependent men and healthy controls using 11C-glucose. Acta Psychiat Scand 78:234–241
48. Gansler DA, Harris GJ, Oscar-Berman M, Streeter C, Lewis RF, Ahmed I et al. (2000) Hypoperfusion of inferior frontal brain regions in abstinent alcoholics: a pilot SPECT study. J Stud Alcohol 61:32–37
49. Melgaard B, Henriksen L, Ahlgren P, Danielsen UT, Sorensen H, Paulson OB (1990) Regional cerebral blood flow in chronic alcoholics measured by single photon emission computerized tomography. Acta Neurol Scand 82:87–93
50. Nicolas JM, Catafau AM, Estruch R, Lomena FJ, Salamero M, Herranz R et al. (1993) Regional cerebral blood flow-SPECT in chronic alcoholism: relation to neuropsychological testing. J Nucl Med 34:1452–1459
51. Valmier J, Touchon J, Zanca M, Fauchere V, Bories P, Baldy-Moulinier M (1986) Correlations between cerebral grey matter flow and hepatic histology in alcoholism. Eur Neurol 25:428–435
52. Hunter R, McLuskie R, Wyper D, Patterson J, Christie JE, Brooks DN et al. (1989) The pattern of function-related regional cerebral blood flow investigated by single photon

emission tomography with 99 mTc-HMPAO in patients with presenile Alzheimer's disease and Korsakoff's psychosis. Psychol Med 19:847–855
53. Shimojyo S, Scheinberg P, Reinmuth D (1967) Cerebral blood flow and metabolism in the Wernicke-Korsakoff Syndrome. J Clin Invest 46:849–854
54. Jagannathan NR, Desai NG, Raghunathan P (1996) Brain metabolite changes in alcoholism: an in vivo proton magnetic resonance spectroscopy (MRS) study. Magn Reson Imaging 14:553–557
55. Pfefferbaum A, Adalsteinsson E, Sullivan EV (2006) Supratentorial profile of white matter microstructural integrity in recovering alcoholic men and women. Biol Psychiatry 59:364–372
56. Pfefferbaum A, Sullivan EV (2005) Disruption of brain white matter microstructure by excessive intracellular and extracellular fluid in alcoholism: evidence from diffusion tensor imaging. Neuropsychopharmacology 30:423–432
57. Courville CB (1964) Forensic neuropathology. XII. The alcohols. J Forensic Sci 9:209–235
58. Harper CG, Kril J (1985) Brain atrophy in chronic alcoholic patients: a quantitative pathological study. J Neurol Neurosurg Psychiatr 48:211–217
59. Harper CG, Kril JL (1990) The neuropathology of alcoholism. Alcohol Alcohol 25:207–216
60. Krill JJ (1995) The contribution of alcohol, thiamine deficiency and cirrhosis of the liver to cerebral cortical damage in alcoholics. Metab Brain Dis 10:9–16
61. Harper CG, Kril JJ, Holloway RL (1985) Brain shrinkage in chronic alcoholics: a pathological study. Br Med J 290:501–504
62. Kril JL, Halliday GM (1999) Brain shrinkage in alcoholics: a decade on and what have we learned? Prog Neurobiol 58:381–387
63. Kril JJ, Halliday GM, Svoboda MD, Cartwright H (1997) The cerebral cortex is damaged in chronic alcoholics. Neuroscience 79:983–998
64. Eisenhofer G, Johnson RH (1982) Effects of ethanol ingestion on plasma vasopressin and water balance in humans. Am J Physiol 242:522–527
65. Harper CG, Kril J, Daly JM (1988) Brain shrinkage in alcoholics is not caused by changes in hydration: a pathological study. J Neurol Neurosurg Psychiatry 51:124–127
66. Tang Y, Pakkenberg B, Nyengaard JR (2004) Myelinated nerve fibres in the subcortical white matter of cerebral hemispheres are preserved in alcoholic subjects. Brain Res 1029:162–167
67. de la Monte SM (1988) Disproportionate atrophy of cerebral white matter in chronic alcoholics. Arch Neurol 45:990–992
68. Jensen GB, Pakkenberg B (1993) Do alcoholics drink their neurons away? Lancet 342:1201–1204
69. Trabert W, Betz T, Niewald M, Huber G (1995) Significant reversibility of alcoholic brain shrinkage within 3 weeks of abstinence. Acta Psychiatr Scand 92:87–90
70. Kril JJ, Harper CG (1989) Neuronal counts from four cortical regions of alcoholic brains. Acta Neuropathol 41:67–80
71. Moselhy HF, Georgiou G, Kahn A (2001) Frontal lobe changes in alcoholism: a review of the literature. Alcohol Alcohol 36:357–368
72. Sullivan EV, Harding AJ, Pentney R, Dlugos C, Martin PR, Parks MH et al. (2003) Disruption of frontocerebellar circuitry and function in alcoholism. Alcohol Clin Exp Res 27:301–309
73. Brun A, Andersson J (2001) Frontal dysfunction and frontal cortical synapse loss in alcoholism – the main cause of alcohol dementia? Dement Geriatr Cogn Disord 12:289–294
74. Cavanagh JB, Holton JL, Nolan CC (1997) Selective damage to the cerebellar vermis in chronic alcoholism: a contribution from neurotoxicology to an old problem of selective vulnerability. Neuropathol Appl Neurobiol 23:355–363

75. Courville CB (1964) Cerebellar degeneration as a consequence of chronic alcoholism. Bull Los Angeles Neurol Soc 29:198–207
76. Karhune PJ, Erkinjuntti T, Laippala P (1994) Moderate alcohol consumption and loss of cerebellar Purkinje cells. Br Med J 308:1663–1667
77. Nicolás JM, Fernández-Solà J, Robert J, Antúnez E, Cofán M, Cardenal C et al. (2000) High ethanol intake and malnutrition in alcoholic cerebellar shrinkage. QJM 93:449–456
78. Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon DH, Lim KO (1998) A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. Arch Gen Psychiatry 55:905–912
79. Torvik A, Torp S (1986) The prevalence of alcoholic cerebellar atrophy. A morphometric and histological study of an autopsy material. J Neurol Sci 75:43–51
80. Phillips SG, Harper CG, Kril J (1987) A quantitative histological study of the cerebellar vermis in alcoholic patients. Brain 110:301–314
81. Andersen BB (2004) Reduction of Purkinje cell volume in cerebellum of alcoholics. Brain Res 1007:10–18
82. Baker KG, Harding AJ, Halliday GM, Kril JJ, Harper CG (1999) Neuronal loss in functional zones of the cerebellum of chronic alcoholics with and without Wernicke's encephalopathy. Neuroscience 91:429–438
83. Bengochea O, Gonzalo LM (1990) Effect of chronic alcoholism on the human hippocampus. Histol Histopathol 5:349–357
84. Harding AJ, Wong A, Svoboda MD, Kril JL, Halliday GM (1997) Chronic alcohol consumption does not cause hippocampal neuron loss in humans. Hippocampus 7:78–87
85. Korbo L (1999) Glial cell loss in the hippocampus of alcoholics. Alcohol Clin Exp Res 23:164–168
86. Baker KG, Halliday GM, Kril JJ, Harper CG (1996) Chronic alcoholics without Wernicke-Korsakoff syndrome or cirrhosis do not lose serotonergic neurons in the dorsal raphe nucleus. Alcohol Clin Exp Res 20:61–66
87. Halliday G, Ellis J, Heard R, Caine D, Harper C (1993) Brainstem serotonergic neurons in chronic alcoholics with and without the memory impairment of Korsakoff's psychosis. J Neuropathol Exp Neurol 52:567–579
88. Halliday G, Ellis J, Harper C (1992) The locus coeruleus and memory: a study of chronic alcoholics with and without the memory impairment of Korsakoff's psychosis. Brain Res 598:33–37
89. Estruch R, Nicolas JM, Salamero M, Aragon C, Sacanella E, Fernandez-Sola J, Urbano-Marquez A (1997) Atrophy of the corpus callosum in chronic alcoholism. J Neurol Sci 146:145–151
90. Pfefferbaum A, Lim KO, Desmond J, Sullivan EV (1996) Thinning of the corpus callosum in older alcoholic men. A magnetic resonance imaging study. Alcohol Clin Exp Res 20:752–757
91. Pfefferbaum A, Adalsteinsson E, Sullivan EV (2006) Dysmorphology and microstructural degradation of the corpus callosum: Interaction of age and alcoholism. Neurobiol Aging 27:994–1009
92. Crews FT, Collins MA, Dlugos C, Littleton J, Wilkins L, Neafsey EJ et al. (2004) Alcohol-induced neurodegeneration: when, where and why? Alcohol Clin Exp Res 28:350–364
93. Randoll LA, Wilson WR, Weaver MS, Spuhler-Phillips K, Leslie SW (1996) *N*-Methyl-D-aspartate-stimulated increases in intracellular calcium exhibit brain regional differences in sensitivity to inhibition by ethanol. Alcohol Clin Exp Res 20:197–200
94. Cullen KM, Halliday GM (1994) Chronic alcoholics have substantial glial pathology in the forebrain and diencephalon. Alcohol Alcohol Suppl 2:253–257

95. Davis RL, Syapin PJ (2004) Ethanol increases nuclear factor-kappa B activity in human astroglial cells. Neurosci Lett 371:128–132
96. Syapin PJ, Hickey WF, Kane CJM (2005) Alcohol brain damage and neuroinflammation: Is there a connection? Alcohol Clin Exp Res 29:1080–1089
97. Vallés SL, Blanco AM, Pascual M, Guerri C (2004) Chronic ethanol treatment enhances inflammatory mediators and cell death in the brain and in astrocytes. Brain Pathol 14:365–371
98. Montoliu C, Sancho-Tello M, Azorin I, Burgal M, Vallés SL, Renau-Piqueras J et al. (1995) Ethanol increases cytochrome P4502E1 and induces oxidative stress in astrocytes. J Neurochem 65:2561–2570
99. Gocht A, Colmant HJ (1987) Central pontine and extrapontine myelinolysis: a report of 58 cases. Clin Neuropathol 6:262–270
100. Kleinschmidt-DeMasters BK, Rojiani AM, Filley CM (2006) Central and extrapontine myelinolysis: then . . . and now. J Neuropathol Exp Neurol 65:1–11
101. Lampl C, Yazdi K (2002) Central pontine myelinolysis. Eur Neurol 47:3–10
102. Newell KL, Kleinschmidt-DeMasters BK (1996) Central pontine myelinolysis at autopsy; a twelve year retrospective analysis. J Neurol Sci 142:134–139
103. Wright DG, Laureno R, Victor M (1979) Pontine and extrapontine myelinolysis. Brain 102:361–385
104. Adams R, Victor M, Mancall E (1959) Central pontine myelinolysis. A hitherto undescribed disease occurring in alcoholic and malnourished patients. Arch Neurol Psychiatr 81:154–172
105. Brown WD (2000) Osmotic demyelination disorders: central pontine and extrapontine myelinolysis. Curr Opin Neurol 13:691–697
106. Norenberg MD, Leslie KO, Robertson AS (1982) Association between rise in serum sodium and central pontine myelinolysis. Ann Neurol 11:128–135
107. Kumar S, Fowler M, Gonzalez-Toledo E, Jaffe SL (2006) Central pontine myelinolysis, an update. Neurol Res 28:360–366
108. Sterns RH, Riggs JE, Schochet SS (1986) Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med 314:1535–1542
109. Haibach H, Ansbacher LE, Dix JD (1987) Central pontine myelinolysis: a complication of hyponatremia or of therapeutic intervention? J Forensic Sci 32:441–451
110. Miller RF, Harrison MJG, Hall-Craggs MA, Scaravilli F (1998) Central pontine myelinolysis in AIDS. Acta Neuropathol 96:537–540
111. Messert B, Orrison WW, Hawkins MJ, Quaglieri CE (1979) Central pontine myelinolysis: considerations on etiology, diagnosis and treatment. Neurology 29:147–160
112. Menger H, Jörg J (1999) Outcome of central pontine and extrapontine myelinolysis. J Neurol 246:700–705
113. Wilske J, Henn R (1983) Zentrale pontine Myelinolyse - Ursache unklarer Todesfälle. In: Barz J, Bösche J, Frohberg H, Joachim H, Käppner R, Mattern R (eds) Fortschritte der Rechtsmedizin. Festschrift für Georg Schmidt. Springer, Berlin Heidelberg New York, pp 123–128
114. Endo Y, Oda M, Hara M (1981) Central pontine myelinolysis. A study of 37 cases in 1,000 consecutive autopsies. Acta Neuropathol 53:145–153
115. Ashrafian H, Davey P (2001) A review of the causes of central pontine myelinosis: yet another apoptotic illness? Eur J Neurol 8:103–109
116. Cravioto H, Korein J, Silberman J (1961) Wernicke's encephalopathy. A clinical and pathological study of 28 autopsied cases. Arch Neurol 4:510–519
117. Halliday G, Cullen K, Harding A (1994) Neuropathological correlates of memory dysfunction in the Wernicke-Korsakoff syndrome. Alcohol Alcohol Suppl 2:245–251
118. Victor M, Adams RD, Collins GH (1971) The Wernicke-Korsakoff syndrome: a clinical and pathological study of 245 patients, 82 with post-mortem examinations. Contemp Neurol Ser 7:1–206

119. Malamud N, Skillicorn SA (1956) Relationship between the Wernicke and the Korsakoff syndrome: a clinicopathologic study of seventy cases. Arch Neurol Psychiatr 76:585–596
120. Kopelman MD (1995) The Korsakoff syndrome. Br J Psychiatr 166:154–173
121. Berger JR (2004) Memory and the mammillothalamic tract. AJNR Am J Neuroradiol 25:906–907
122. Torvik A (1987) Topographic distribution and severity of brain lesions in Wernicke's encephalopathy. Clin Neuropathol 6:25–29
123. Torvik A (1985) Two types of brain lesions in Wernicke's encephalopathy. Neuropathol Appl Neurobiol 11:179–190
124. Harper C, Butterworth R (2002) Nutritional and metabolic disorders. In: Graham DI, Lantos PL (eds) Greenfield's neuropathology, 7th edn. Arnold Publishers, London, pp 607–652
125. Harding A, Halliday G, Caine D, Kril J (2000) Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. Brain 123:141–154
126. Shear PK, Sullivan EV, Lane B, Pfefferbaum A (1996) Mammillary body and cerebellar shrinkage in chronic alcoholics with and without amnesia. Alcohol Clin Exp Res 20:1489–1495
127. Visser PJ, Krabbendam L, Verhey FRJ, Hofman PAM, Verhoeven WMA, Tuinier S et al. (1999) Brain correlates of memory dysfunction in alcoholic Korsakoff's syndrome. J Neurol Neurosurg Psychiatr 67:774–778
128. Victor M (1987) The irrelevance of mammillary body lesions in the causation of the Korsakoff amnesic state. Int J Neurol 21/22:51–57
129. Harper C (1983) The incidence of Wernicke's encephalopathy in Australia – a neuropathological study of 131 cases. J Neurol Neurosurg Psychiatr 46:593–598
130. Harper CG, Giles M, Finlay-Jones R (1986) Clinical signs in the Wernicke-Korsakoff complex: a retrospective analysis of 131 cases diagnosed at necropsy. J Neurol Neurosurg Psychiatr 49:341–345
131. Naidoo DP, Bramdev A, Cooper K (1996) Autopsy prevalence of Wernicke's encephalopathy in alcohol-related disease. S Afr Med J 86:1110–1112
132. Thomson AD (2000) Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. Alcohol Alcohol Suppl. 35:2–7
133. Charness ME (1993) Brain lesions in alcoholics. Alcohol Clin Exp Res 17:2–11
134. Rodda R, Cummings R, Milligens KS (1978) Wernicke-Korsakov syndrome lesions in coronial necropsies. Clin Exp Neurol 15:114–126
135. Butterworth RF (2003) Hepatic encephalopathy. Alcohol Res Health 27:240–246
136. Lewis M, Howdle PD (2003) The neurology of liver failure. QJM 96:623–633
137. Lizardi-Cervera J, Almeda P, Guevara L, Uribe M (2003) Hepatic encephalopathy: a review. Ann Hepatol 2:122–130
138. Vaquero J, Chung C, Cahill ME, Blei AT (2003) Pathogenesis of hepatic encephalopathy in acute liver failure. Semin Liver Dis 23:259–269
139. Blei AT, Larsen FS (1999) Pathophysiology of cerebral edema in fulminant hepatic failure. J Hepatol 31:771–776
140. Norenberg MD (1998) Astroglial dysfunction in hepatic encephalopathy. Metab Brain Dis 13:319–335
141. Häussinger D, Kircheis G, Fischer R, Schliess F, vom Dahl S (2000) Hepatic encephalopathy in chronic liver disease: a clinical manifestation of astrocyte swelling and low-grade cerebral edema? J Hepatol 32:1035–1038
142. Kato M, Hughes RD, Keays RT, Williams R (1992) Electron microscopic study of brain capillaries in cerebral edema from fulminant hepatic failure. Hepatology 15:1060–1066
143. Kimura T, Budka H (1986) Glial fibrillary acidic protein and S-100 protein in human hepatic encephalopathy: immunoyctochemical demonstration of dissociation of two glia-associated proteins. Acta Neuropathol 70:17–21

144. Sobel RA, De Armond SJ, Forno LS, Eng LF (1981) Glial fibrillary acidic protein in hepatic encephalopathy. An immunohistochemical study. J Neuropathol Exp Neurol 40:625–632
145. Kohler CG, Ances BM, Coleman AR, Ragland JD, Lazarev M, Gur RC (2000) Marchiafava-Bignami disease: literature review and case report. Neuropsychiatr Neuropsychol Behav Neurol 13:67–76
146. Jellinger K (1961) Marchiafava-Bignami-Syndrom. Acta Neuropathol 1:101–104
147. Cook CC, Hallwood PM, Thomson AD (1998) B Vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. Alcohol Alcohol 33:317–336
148. Serdaru M, Hausser-Hauw C, Laplane D, Buge A, Castaigne P, Goulon M et al. (1988) The clinical spectrum of alcoholic pellagra encephalopathy. A retrospective analysis of 22 cases studied pathologically. Brain 111:829–842
149. Hauw JJ, De Baecque C, Hausser-Hauw C, Serdaru M (1988) Chromatolysis in alcoholic encephalopathies. Pellagra-like changes in 22 cases. Brain 111:843–857
150. Ishii N, Nishihara Y (1981) Pellagra among chronic alcoholics: clinical and pathological study of 20 necropsy cases. J Neurol Neurosurg Psychiatr 44:209–215
151. Hillbom M, Juvela S, Numminen H (1999) Alcohol intake and the risk of stroke. J Cardiovasc Risk 6:223–228
152. Leppävuori A, Vataja R, Pohjasvaara T, Kaste M, Mäntylä R, Erkinjuntti T (2003) Alcohol misuse: a risk factor for putaminal damage by ischemic brain infarct? Eur Neurol 50:69–72
153. Camargo CA Jr (1989) Moderate alcohol consumption and stroke. The epidemiologic evidence. Stroke 20:1611–1626
154. Hillbom M, Kaste M (1982) Alcohol intoxication: a risk factor for primary subarachnoid hemorrhage. Neurology 32:706–711
155. Dick DM, Foroud T (2003) Candidate genes for alcohol dependence: a review of genetic evidence from human studies. Alcohol Clin Exp Res 27:868–879
156. Dodd PR, Foley PF, Buckley ST, Eckert AL, Innes DJ (2004) Genes and gene expression in the brain of the alcoholic. Addict Behav 29:1295–1309
157. Worst TJ, Vrana KE (2005) Alcohol and gene expression in the central nervous system. Alcohol Alcohol 40:63–75
158. Anni H, Israel Y (2002) Proteomics in alcohol research. Alcohol Res Health 26:219–232