The Neuropathology of Alcohol-Related Brain Damage

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Abstract — Excessive alcohol use can cause structural and functional abnormalities of the brain and this has significant health, social and economic implications for most countries in the world. Even heavy social drinkers who have no specific neurological or hepatic problems show signs of regional brain damage and cognitive dysfunction. Changes are more severe and other brain regions are damaged in patients who have additional vitamin B1 (thiamine) deficiency (Wernicke–Korsakoff syndrome). Quantitative studies and improvements in neuroimaging have contributed significantly to the documentation of these changes but mechanisms underlying the damage are not understood. A human brain bank targeting alcohol cases has been established in Sydney, Australia, and tissues can be used for structural and molecular studies and to test hypotheses developed from animal models and in vivo studies. The recognition of potentially reversible changes and preventative medical approaches are important public health issues.

REVIEW

It has long been accepted that excessive alcohol use can cause structural and functional abnormalities of the brain and other organs (Courville, 1955; Victor et al., 1959; Dreyfus and Victor, 1961). In the brain, this has been demonstrated clinically, with imaging techniques and pathologically. Many alcoholics can also develop cirrhosis of the liver that can impact on brain structure and function and others develop nutritional deficiency states (vitamin B1 deficiency) that can cause severe brain damage and dysfunction. These latter two groups of alcoholic cases are often defined as ‘complicated alcoholics’ to differentiate them from those who do not have liver disease or nutritional deficiency states (uncomplicated alcoholics). Nevertheless, ‘uncomplicated alcoholics’ who are cognitively impaired have abnormalities (Pfefferbaum et al., 1997). The risks of ‘moderate’ alcohol consumption are more difficult to assess. Ding and colleagues showed that the more alcohol consumed, the larger the cerebrospinal fluid-filled spaces of the brain became (Ding et al., 2004). This data correspond with a neuropathological study that showed an increase in the cerebrospinal fluid-filled spaces covering the brain (pericerebral space) in men drinking more than eight standard drinks per day and a similar distinctive trend in those drinking five to eight standard drinks per day (Harper et al., 1988). However, in a detailed volumetric analysis of high resolution MRI scans of ‘moderate’ drinkers, de Bruin and colleagues showed that neither current nor lifetime alcohol intake is associated with decreases in brain volumes in male or female moderate drinkers (de Bruin et al., 2005). They defined their male moderate drinkers as those with a current alcohol intake of approximately three drinks per week and a lifetime alcohol intake of 240 kg. The varying definitions of ‘moderate’ obviously explain some of the discrepancies in these pathological and imaging studies.

There have been very few recent neuropathological studies on the subject of alcohol-related brain damage. This may reflect difficulties with access to pathological material, given the worldwide decline in hospital autopsy rates (Ward et al., 2002). A unique ‘brain bank’ (New South Wales Tissue Resource Centre—http://www.pathology.usyd.edu.au/trc.htm) has been established in Australia during the last decade to address this problem. The aim is to provide tissues (fresh-frozen and formalin-fixed) to research groups throughout the world. The majority of studies supported in the last few years have been molecular (Harper et al., 2002, 2003). An additional ‘tool’ that can be used in these cases is the acquisition of MRI images of the postmortem brain (Pfefferbaum et al., 2004). These high-resolution images provide archival images that can be reformatted in different axes before permanent sectioning. Postmortem imaging provides a technique to explore and quantify discrepancies between in vivo results and postmortem. The technique has been used effectively in the study of Alzheimer’s disease (Bronge, 2002). Moreover, as ‘in life’ brain donor programmes expand (http://www.braindonors.org), there will be opportunities for donors to have premortem MRIs. These will provide additional sets of data points that will be available for researchers using brain bank material.

From a neuropathological point of view, papers describing structural changes in the human brain caused by alcohol were first published in the 1980s as reliable automated quantitative analytical methods for volume measurements and cell counts became available (Terry and DeTeresa, 1982). However, there had been considerable interest in alcohol-associated conditions like the Wernicke–Korsakoff syndrome (WKS) and cerebellar cortical degeneration well before, since there were specific clinical syndromes that could be recognized by neurologists (Victor et al., 1959, 1971) and psychiatrists (Wernicke, 1881).

The first quantitative neuropathological study on brain weights in alcoholics (Harper and Blumbergs, 1982) was inspired by the various reports of ‘brain shrinkage’ seen on CT scans in alcoholics (Cala et al., 1978; Ron et al., 1980). Alcoholics have a reduced brain weight compared to controls and the degree of brain atrophy has been shown to correlate with the rate and amount of alcohol consumed over a lifetime (Harding et al., 1996). An unexpected pathological finding was that the reduction in brain volume was largely accounted for by a reduction in white matter volume (Harper and Kril, 1985; De la Monte, 1988). This was also shown in an animal model (dog) (Hansen et al., 1991). However, these data conflict with many quantitative MRI analyses in alcoholics that have shown that the cortical grey matter is also reduced in volume (Pfefferbaum et al., 1995; Mann et al., 2001). The explanation for this discrepancy may relate to the many changes that occur postmortem.
White matter changes

Kril and colleagues noted that the prefrontal white matter was most severely affected in alcoholics with the WKS. Moreover, there was a negative correlation between the white matter loss and the maximum daily alcohol consumption (Kril et al., 1997). The corpus callosum is the major white matter commissure connecting the cerebral hemispheres and it allows interhemispheric exchange of sensory, motor and cognitive information. Pathological (Harper and Kril, 1988; Tarnowska-Dziduszko et al., 1995) and imaging studies (Pfefferbaum et al., 1996; Estruch et al., 1997) have shown that the volume of the corpus callosum is significantly reduced in alcoholics, especially those with nutritional deficiencies (Lee et al., 2005). DTI (diffusion tensor imaging) studies suggest that there is disruption of the microstructural integrity of the corpus callosum (Schulte et al., 2005; Pfefferbaum et al., 2006a). There appears to be a correlation between these structural changes and cognitive performance (Chanraud et al., 2007). The volume of white matter of the cerebellum is also reduced in alcoholics (Phillips et al., 1987; Sullivan et al., 1998). This seems particularly relevant, given the interest and potential importance of the cerebellum in executive function (Schmahmann and Sherman, 1998), and Sullivan and colleagues have shown that cerebellar-cerebral loops are targeted by alcoholism (Sullivan, 2003). Microscopically, there are no obvious white matter lesions in the cerebral hemispheres of uncomplicated alcoholics and studies of lipid profiles have revealed only minor alterations (Harper et al., 1991; Olsson et al., 1996). The subtle nature of alcohol-related white matter changes in the cerebral hemispheres are borne out by the relative normality of other physical and chemical analyses of white matter (Harper, 1998). It has been suggested that reversible white matter loss could be caused by changes in hydration but neurochemical (Trabert et al., 1995) and imaging studies (Mann et al., 1992) refute this hypothesis. Wiggins and colleagues reported an acceleration of normal age-related myelin loss in humans with a heavy alcohol consumption but analysis of the myelin composition showed no changes (Wiggins et al., 1988).

Although the nature of alcohol-related white matter loss has not yet been elucidated, it is likely that the disruption involves changes in both myelination and axonal integrity (Harper and Matsumoto, 2005; Pfefferbaum and Sullivan, 2005). Ultrastructural studies of human postmortem material are not possible because of the rapid degradation of myelin membranes after death. However, they can be observed in animal models. Phillips and his colleagues showed that alcohol causes a permanent reduction in the relative thickness of myelin sheaths in the developing rat optic nerve (Phillips et al., 1991). This would certainly have the potential to cause significant neurological dysfunction. Changes in both axons and myelin were noted in a recent animal experiment designed to differentiate the separate and combined effects of thiamine deficiency and voluntary alcohol consumption. The corpus callosum in the alcohol/pyrithiamine group of rats was significantly thinner, had greater fibre density, higher percentage of small fibres and myelin thinning than in the alcohol/thiamine and water/thiamine groups. Several measures showed a graded effect, where the alcohol/pyrithiamine group had greater pathology than the water/pyrithiamine group, which had greater pathology than the two thiamine-replete groups. This suggests a compounding effect of chronic alcohol exposure and thiamine depletion in human alcohol-related brain damage (He et al., 2007).

As noted above, the mechanism for alcoholism-related white matter loss, restoration with alcohol abstinence and disruption of micro structural integrity still remains unclear but probably involves changes in both myelination and axonal integrity. This has been inferred from in vivo human and experimental MR diffusion tensor imaging studies (Pfefferbaum et al., 2006b, 2007) and may explain why tissue volume recovery appears incomplete with abstinence. Thus, alcoholic brain pathology may have two components, one reflecting permanent change and one a transient change. Regarding permanent effects, alcohol-related neuronal loss has been documented in specific regions of the cerebral cortex (superior frontal association cortex), hypothalamus and cerebellum (Harper, 1998). Such loss will result in axonal (Wallerian) degeneration and a permanent reduction in white matter volume. Structural changes in myelin, however, could explain the reversible white matter shrinkage that has been documented with serial MRI studies following periods of abstinence from alcohol (Shear et al., 1994; Pfefferbaum et al., 1995; Gazdzinski et al., 2005). Bartsch and colleagues, using a combination of MRI and MR spectroscopy, have shown that volumetric brain gain was related to metabolic and neuropsychological recovery (Bartsch et al., 2007). There were significant increases of cerebellar choline and frontomesial N-acetylaspartate levels suggesting that the human brain and particularly its white matter possess capabilities for regrowth. Their findings emphasize metabolic as well as regionally distinct morphological capacities for partial brain recovery from toxic insults of chronic alcoholism (Bartsch et al., 2007). Functional sequelae of alcoholism that improve or reverse with abstinence include impairment in working memory, postural stability and visuospatial ability (Sullivan et al., 2000b; Rosenbloom et al., 2004). Another brain region that warrants further investigation regarding specific cognitive deficits is the amygdala. Fein and Landman noted atrophy in the amygdala in long-term abstinent alcoholics and suggested that it could be the anatomic correlate for impaired decision making (Fein et al., 2006).

Cases from the Australian ‘brain bank’ have been used for molecular studies to try to identify the mechanisms causing reversible ‘shrinkage’. Lewohl and colleagues used DNA microarray technology and showed that the expression of three genes encoding myelin proteins was decreased in the superior frontal cortex of human alcoholic subjects (Lewohl et al., 2005). In addition there were changes in several cell cycle and neuronal genes. The difference in gene expression was most pronounced for PLP, one of the major myelin proteins in the CNS. PLP and MBP are required for the highly ordered and compact structure of myelin and are specifically involved in stabilization and compaction of the myelin sheath (Weimbs and Stoffel, 1992; Boison and Stoffel, 1994). Any alterations are likely to alter the structure and function of the myelin sheath and ultimately the conduction of action potentials. These data clearly demonstrate the power of using high throughput analyses to provide clues to the pathophysiology of these complex disorders. More recently, a complete 2D PAGE proteomic map of myelin proteins in mouse CNS was established (Taylor et al., 2004) and the application of a similar methodology to study the neuropsychiatric diseases using human brain samples is now possible.
Neuronal changes in alcohol-related disorders

Neuronal loss has been documented in specific regions of the cerebral cortex (superior frontal association cortex), hypothalamus and cerebellum in alcoholics (Harper et al., 1987; Harding et al., 1996; Baker et al., 1999). Analysis of the types of neurons lost from the frontal cortex revealed that they were the larger ones with a somal area >90 μm (Harper and Kril, 1989). This population of neurons is also more vulnerable in both Alzheimer’s disease (Terry et al., 1981) and normal aging (Terry and Hansen, 1987). There does not appear to be any link between alcohol-related brain damage and Alzheimer’s disease (Morikawa et al., 1999), although there is some work that suggests a relationship between alcohol and aging (Harper and Corbett, 1990). An important point to note is that this dendritic shrinkage has been shown to be reversible in an experimental model following a prolonged period of abstinence (McMullen et al., 1984). This finding has obvious functional implications regarding the documented reversibility of cognitive deficits in abstinent alcoholics (Sullivan et al., 2000b). There is some indirect molecular evidence that cytoskeletal proteins are affected by alcohol. Using human brain bank material, Fan and Depaz and colleagues identified and cloned a novel human gene (hNP22) that is only found in the brain and is specific to neurons (Depaz et al., 2003). There is increased expression of hNP22 in both superior frontal cortex and hippocampus of alcoholic subjects (Fan et al., 2001; Depaz et al., 2003). It is an actin-binding protein and there is some homology with calponin and human protein SM22, both of which can bind elements of the cytoskeleton. The increased expression of hNP22 in the frontal cortex and hippocampus may reflect an adaptive change to chronic alcohol exposure that may lead to changes of neuronal plasticity.

Cerebellum

Atrophy of the cerebellum is commonly associated with alcoholism. Torvik and colleagues reported that 26.8% of alcoholics with WKS had cerebellar atrophy (Torvik and Torp, 1986). Neuroimaging in vivo (Sullivan et al., 2000a) and examination of the cerebellum at autopsy reveal shrinkage of the anterior superior cerebellar vermis. Quantitative pathological studies have shown that there is a loss of Purkinje cells in the vermis (reduced on average by 43%) that correlates with clinical ataxia/unsteadiness (Baker et al., 1999). They also noted a correlation between the loss of Purkinje cells in the lateral lobes of the cerebellum and ‘mental signs’. This is particularly interesting given the recent speculation that the cerebellum is important in the organization of higher cerebral functions (Schmahmann and Sherer, 1998; Sullivan, 2003). Baker and colleagues (Baker et al., 1999) showed that there is no consistent correlation between the number of neurons or the structural volume for any of the cerebellar regions in uncomplicated chronic alcoholics. This suggests that chronic alcohol consumption alone does not necessarily damage human cerebellum. However, significant changes were noted in alcoholics with the WKS suggesting that the damage in the cerebellum is caused by thiamin deficiency.

There has always been some confusion about the diagnostic categories of Wernicke’s encephalopathy and Korsakoff’s psychosis. They are commonly referred to as the WKS. The two disorders are commonly seen in alcoholics and are dramatically different clinically but the neuropathology was thought to be identical for many years (Victor et al., 1989). Korsakoff patients have a severe amnesic syndrome with or without the classical signs of Wernicke’s encephalopathy (confusion, ataxia and ophthalmoplegia/nystagmus). New operational criteria for the diagnosis of Wernicke’s encephalopathy have been formulated by Caine and colleagues (Caine et al., 1997). Two of the following should be present: dietary deficiency, oculomotor abnormalities, cerebellar dysfunction and either altered mental state or mild memory impairment. It has been suggested that the two disorders are a continuum (Feinberg, 1980; Butters and Brandt, 1985). The pattern of neuropathological changes was described best by Victor and Adams (Victor et al., 1971). Lesions tend to be in periventricular regions, particularly around the third and fourth ventricles. The explanation for this restrictive topography is still unclear. They were unable to differentiate pathologically between Wernicke’s encephalopathy and Korsakoff’s psychosis in spite of dramatic differences in clinical presentations. It was only when quantitative analyses of diencephalic structures were completed by Harding and his colleagues that differences were identified that account for Korsakoff’s psychosis—damage to the anterior nucleus of the thalamus (Harding et al., 2000). It was noted that patients with non-amnesic Wernicke’s encephalopathy also have damage in these regions, but it is less severe. Combined neuropsychology/neuroimaging studies suggest that the amnesia is probably caused by interruption of complex diencephalic–hippocampal circuitry including thalamic nuclei and mamillary bodies rather than a single lesion in the anterior thalamic nucleus (Sullivan and Marsh, 2003). Quantitative studies also showed that many of the changes discussed above in the section on the structural changes caused by alcohol are exacerbated by thiamine deficiency and in fact, it seems that thiamine deficiency is the principle factor causing brain damage in alcoholics (Harper, 1998, 2007; Harper and Matsumoto, 2005). It has been clear for many years that the WKS is caused by thiamine deficiency and a number of links between alcohol and thiamine metabolism explain the frequency of the disorder in the alcoholic population (Harper, 2006). Recently, proteomics studies have shown that thiamine metabolism might be altered even in ‘uncomplicated alcoholics’ with no evidence of the WKS. Protein expression profiles of cortical area BA9 grey and white matter and the cerebellar vermis showed changes in the levels of a number of thiamine-dependent enzymes (Alexander-Kaufman et al., 2006, 2007).

The WKS is still a worldwide problem and cases are reported regularly in medical journals from every country in the world. Many of the patients have a history of alcohol abuse but others are caused by poor nutrition, long-term parenteral feeding, gastrectomy, diets, AIDS, hyperemesis gravidarum and others (Harper, 2006). The Royal College of Physicians (London) recommends that patients admitted to A&E, who show evidence of chronic alcohol misuse and are suspected of having a poor diet, should be treated with B vitamins (Thomson et al., 2002).
They emphasised that the clinical signs are often masked by drunkenness. Regardless of the cause, the prevalence of the WKS can be reduced by the supplementation of our diets with thiamin in stable foods like bread. This has been done in a number of countries for many years (USA, UK, Australia) with great success (Harper et al., 1998b). This should be considered by the health departments in all countries where alcohol-related disorders are common.

**Prevention and education**

Studies of alcohol-related brain damage, particularly risk factors and proposed mechanisms of action, are critical tools that can be applied in public education programmes. The identification of pathological changes in the brain that might be reversible is very important information to convey to the public as it could assist in rehabilitation programmes. Moreover, it should also be communicated to the medical community as it could enhance preventative medical approaches and treatment efforts, thereby mitigating the debilitating morbidities and reducing mortality associated with this universal public health problem.

**REFERENCES**


