Histopathological and imaging modifications in chronic
ethanolic encephalopathy

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Abstract
Chronic abuse of alcohol triggers different types of brain damage. The Wernicke–Korsakoff syndrome gets together Wernicke’s encephalopathy and Korsakoff’s syndrome. Another type of encephalopathy associated with chronic ethanol consumption is represented by the Marchiafava–Bignami malady or syndrome, an extremely rare neurological disorder, which is characterized by a demielinization of corpus callosum, extending as far as a necrosis. Because the frequency of ethanolic encephalopathy is increased and plays a major role in the sudden death of ethanolic patients, we have studied the chronic ethanolic encephalopathy both in deceased and in living patients, presenting different pathologies related to the chronic ethanol consumption. The present study investigated the effects of chronic ethanolic encephalopathy on the central nervous system based both on the histopathological exam of the tissular samples and the imaging investigation, such as MRI and CT.

Keywords: ethanolic encephalopathy, corpus callosum, Marchiafava–Bignami syndrome, MRI, CT diagnosis.

Introduction
The term of encephalopathy refers to a group of disorders characterized by a deep alteration of the cerebral structures and functions. The encephalopathy represents the consequence of some severe diseases, infections or the consequence of alcohol or drug abuse and can vary in severity from discrete, subtle modifications of mental state until a more advanced state than can lead to deep coma or even death [1]. There is no available statistical information about the encephalopathy, which can occur at any age, as long as there is no gender or racial predilection, the encephalopathy being a manifestation of a primary disease [2–4].

The definitive diagnoses can be problematic in some circumstances and it is based on the neuroimaging studies, particularly the MRI and the CT [5].

The treatment of this disorder is still controversial and has variable results [6]. If the disease is not treated, it can frequently lead to a permanent brain damage. Because the storage and the metabolic thiamin pathway are deeply affected by the ethanol chronic consumption, a promptly thiamine administration is helpful, limiting the tissular alterations or preventing the rapid decompose [7].

Aim
Our study intends to highlight the most significant histopathological and neuroimaging alterations in chronic ethanolic encephalopathy, making mention of a case of a Marchiafava–Bignami syndrome, due to the rarity of this disorder and the difficulty in exploring and determine a precocious diagnosis.

Materials and Methods
The histopathological study was performed on tissular samples gathered from the Institute of Legal Medicine Timişoara, Romania, from 790 deceased patients with chronic ethanolic encephalopathy. The statistical analysis taken into account was carried on a period of five years (2008–2012) on 790 cases. The prelevated samples were specifically treated for paraffin embedding and were stained with Hematoxylin–Eosin (HE). The microscopic exam was performed using an Olympus optical microscope.

The CT helical scan, followed by MRI examination highlighted, were also used to detect and to reveal the impact of chronic alcohol consumption on cerebral tissues.

In the case of Marchiafava–Bignami suspected syndrome, we have examined a 42-year-old female patient with chronic alcohol abuse, loss of 24 kg in weight in the last three months, who presented a severe acute state of the disease. The patient presented an alteration of its general status, with severe depression, conscious state perturbance, apraxia, temporo-spatial disorganization and light cephalgia. General state alteration and the depressive syndrome imposed the carrying of a cerebral CT, followed by a MRI investigation, using the FLAIR FAT SAT, Diffusion Weighted Image (DWI) and Apparent Diffusion Coefficient (ADC) map.

Results
Out of a total number of 790 chronic ethanolic patients deceased, we observed that the most frequently associated pathology is consisting of myocardial fibrosis, myocardial infarction and hepatic cirrhosis. Acute ethanolic intoxication, followed by death in ethanol dependent patients is rare (Figure 1).
Figure 1 – Incidence of histopathological changes of nervous disorders in ethanolic encephalopathy based on death causes.

Cerebral edema concerns both white and gray matter, with a predilection for the white matter. Into the white matter, cerebral edema causes the astrocyte prolongation swelling and enlargement of extracellular spaces. Granulovascular dystrophy of neurons (intracellular edema) appears, and also the perivascular and perineuronal spaces distension. In massive cerebral edema, there is a marked chromatolysis, nuclear pyknosis and neurophagy. Myelinated nervous fibers break away, especially those around blood vessels; the astrocyte hypertrophy, the oligodendroglia swells and presents homogenization of the nuclei and acidophilia. The nervous tissues become alveolar or cribriform – spongy cerebral tissue (Figure 2).

Vascular alterations are primary, constant, determining vacuolization, determining the increase of permeability and secondary parenchyma modifications. Subsequently, a disintegration of nervous fibers and myelin takes place, associated with a glial reaction. The toxic factor, alcohol, alters the metabolic functions of the cells, especially the astrocytes, causing their swelling. Pericellular and perivascular edema determines vessel compression (Figure 3).

Microscopic lesions in Korsakoff’s syndrome and Wernicke’s encephalopathy are represented by hypoxic degeneration foci, without inflammatory reaction, symmetrically and elective situated at the level of neurovegetative centers in the lateral ventricles, mammillary bodies and fornix, in the posterior hypothalamic nuclei and around the Sylvius aqueduct, where upon nevroglial and vascular proliferation adds up. Later, a reduced number of neurons in the 3rd and 5th layer of the cerebral cortex is identified (Figure 4).

In delirium tremens, a cerebral edema and congestion was noticed, with permeability disorder, plasmatic and hematic perivascular extravasation, prevalent in diencephalon and mesencephalon. In alcoholic dementia, the following disorders occurred: cortical atrophy, corpus callosum body atrophy, vascular degenerative lesions and glial proliferation. In general, alcoholic pseudoparalysis there were identified vascular lesion with pericapillary hemorrhage (Figure 5), together with degenerative lesions of mammillary bodies and corpus callosum, which can lead to sudden death.

Figure 2 – Spongy aspect of the cerebral tissue. HE staining, ×400.

Figure 3 – Intense perivascular edema. HE staining, ×400.

Figure 4 – Hypoxic degeneration around Sylvius aqueduct. HE staining, ×400.

Figure 5 – Perivascular hemorrhagic suffusions. HE staining, ×400.
The Marchiafava–Bignami syndrome was characterized by a central degeneration of corpus callosum, presenting initial microscopic demielinization lesions, followed by necrosis (Figure 6). Laminar cortical sclerosis of Morel is histological characterized by a massive disappearance of pyramidal neurons of the 3rd cortical layer, a glial proliferation and a corpus callosum necrosis (Figure 7). CT exam shows focal hypodense lesion at the level of splenium of corpus callosum (Figures 8–10), while the MRI (Figures 11–15) exam highlight focal cortical hyperintense areas in DWI and FLAIR sequence, at the level of white matter and the semioidal center, without mass effect.
Discussion

Chronic ethanolic encephalopathy comprises two separate sets of disorders revealed in case of Wernicke’s and Korsakoff’s syndrome [8, 9]. Wernicke’s encephalopathy is a neuropsychic disorder, which is owed to the lack of B1 vitamin in alimentation or chronic alcoholism, which inhibits the absorption and metabolization of thiamin [10–12].

Wernicke’s encephalopathy implies both central nervous lesions and also peripheral nervous system lesions that can lead to Korsakoff’s psychosis. This type of dementia can be extremely debilitating, leading to coma or death [13]. In 1881, Wernicke pointed out the “classical triad” of Wernicke’s signs and symptoms: oculomotor abnormality (ophthalmoplegia), cerebellum dysfunction and confusion. Nevertheless, Clive Harper and its group have demonstrated that only 16.5% of the patients presented all the signs and many patients presented only confusions [14]. Neuroimaging study can be helpful, because in many chronic cases, MRI shows mammillary bodies’ atrophy and third ventricle expansion [15].

Marchiafava–Bignami (MBD) syndrome represents another type of encephalopathy associated with chronic alcohol consumption. It is one of the most rare neurological disorders which was observed in alcoholic and malnourished patients, characterized by a demielinization and atrophy, followed by corpus callosum necrosis in the later stage [16, 17]. MBD in non-alcoholic without malnutrition patients was extremely rare reported. MBD is the result of B vitamin group and folic acid deficit [18]. MBD was first pointed out at wine drinkers in Italy 110 years ago. In the beginning, MBD was considered as being particular to the persons living in the central region of Italy, who were drinking an increased quantity of Chianti wine. A vast majority of patients were male between 40 and 60-year-old, having chronic alcohol antecedents and malnutrition [8, 19, 20]. The disease is seen only occasionally in non-alcoholic individuals, it has not any racial predilection and in many cases remains undiagnosed [21–25]. Neuropsychological deficits have also to be noticed.

In 2004, Heinrich et al. described two clinical subtypes based on imaging examination carried out on more than 50 cases, diagnosed in vivo. Type A had clinical characters of coma and stupor. This subtype is associated with a higher rate of pyramidal tract symptoms. The imaging characteristic exam included corpus callosum diffuse lesions. Type B is characterized by normal mental status or slight disturbance. The characteristic imaging exam includes partial or focal corpus callosum lesions [22, 23, 26].

In the medical data, starting in 1903, until 2001 there have been pointed out a number of approximately 500 cases of MBD cases, and more than 90% of them presented a weak prognosis. MBD presents a high degree of mortality and morbidity, thus in 2004, out of 250 patients, 200 died, 30 have suffered a severe dementia and only 20 cases were partially cured [8].

Until the discovery of modern imaging methods, a definitive diagnose was highlighted only after autopsy. Nowadays, we can confirm the diagnosis by using the clinical profile of the alcoholic patient with CT and MRI techniques, which can demonstrate specific pathological lesions in corpus callosum [22, 24, 27]. Corpus callosum appears hypodense on CT scans and hyperintense on MRI/DWI sequences, with the only exception where subacute hemorrhage were noticed, where the lesions appeared as isodense or hyperdense on CT scans [28]. Nevertheless, when the lesion is small, on CT scans it tends to appear as normal parenchyma. In those cases, the MRI exam has a higher sensitivity [29]. In our study, the CT helical scan, followed by MRI examination highlighted symmetrical cerebral structures, without any sign of expansive soft tissue lesions, no hemorrhagic or ischemic lesions, with only a hypodense CT lesion and a hyperintense DWI and ADC map in the posterior region of corpus callosum, without any circumscribed expansive lesion at this level. An enlargement of lateral ventricles and also of the cortical sulci was noted, in relation with the patient’s age.

The increase of MRI availability facilitated the discovery of incipient cases presenting MBD, with partial involvement of corpus callosum. MRI brought information regarding corpus callosum lesions (focal or diffuse, reversible or persistent) and led to the discovery of cortical involvement in some MBD cases, in the vast majority of those cases with poor prognosis [30]. Despite the great advances in imaging investigations, there is still a firm opinion regarding the importance of the clinical diagnosis for a promptly therapeutic intervention.

The etiology of this disorder is uncertain, without a specific and well-defined treatment available. Treatment with B vitamin group (thiamin), including B12 vitamin and folic acid have been used in many cases in patients who have later recovered [23, 24]. The therapy intends to correct the nutritional deficiency of thiamin, thus facilitating its transport across the blood-brain barrier. Nevertheless, the therapeutic failure is not less frequent, even though treatment is started in an early stage of symptoms, while convulsions and come are treated symptomatically [25, 26].

In our case, the female patient received high doses of intravenous and parenteral thiamin and folic acid, noticing a slight and gradual recuperation of her health state. The patient was held under medical surveillance and was administered 1000 mg/day intravenous thiamin for two weeks, then 200 mg/day for five weeks, folic acid 30 mg/day, adequate counseling and treatment for alcohol abuse, dietetic regime and following the rehabilitation therapy a mildly improvement has been noticed (Glasgow 10).

Some previous studies suggested that the risk factors, such as the rate and severity of clinical progression, as well as corpus callosum lesions up against extra-callosal lesions can have prognostic value. Subsequently, those notions were contested because the acute and subacute MBD cases do not necessary have a fatal result, some of the patients surviving and even having a favorable prognosis, with light sequel in a few month time. In addition, amelioration after symptomatic treatment could be noticed in our patient. Thus, is incorrect to assign a prognosis value on the extra-callosal involvement following MRI results [30, 31].
In virtue of the history, clinical data and imaging results using CT and MRI scans, the patient presenting characteristic corpus callosum lesions has been diagnosed with Marchiafava–Bignami syndrome or disease. Sudden death due to central nervous system lesions appear only in acute intoxications associated with other degenerative chronic lesions of different organs, including the neurons. The association with heart and liver disorder is frequent. Therefore, the symptomatic treatment of those organs can increase the survival duration of the patients.

References


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