Introduction

Encephalopathy is an acute confusional state that is accompanied by an alteration in the level of consciousness (drowsiness, stupor, or coma). The term often used interchangeably with delirium **(Aminoff, 2011)**.

It can be due to direct injury to the brain, or illness remote from the brain. In medical terms it can refer to a wide variety of brain disorders with very different etiologies, prognosis and implications. For example, prion diseases (neurodegenerative diseases that have long incubation periods and progress inexorably once clinical symptoms appear), all of which cause transmissible spongiform encephalopathies, are invariably fatal, but other encephalopathies are reversible and can be caused by nutritional deficiencies, toxins, and several other causes **(Müller et al., 2008)**.

The hallmark of encephalopathy is an altered mental state. Depending on the type and severity of encephalopathy, common neurological symptoms are loss of cognitive function, subtle personality changes, inability to concentrate, lethargy, and depressed consciousness. Other neurological signs may include myoclonus (involuntary twitching of a muscle or group of muscles), asterixis (abrupt loss of muscle tone, quickly restored), nystagmus (rapid, involuntary eye movement), tremor, seizures, jactitation (restless picking at things characteristic of severe infection), and respiratory abnormalities such as Cheyne-Stokes respiration (cyclic waxing and waning of tidal volume), apneustic respirations and post-hypercapnic apnea. Blood tests, spinal fluid examination by lumbar puncture, imaging studies, electroencephalograms

and similar diagnostic studies may be used to differentiate the various causes of encephalopathy. Diagnosis is frequently clinical. That is, no set of tests give the diagnosis, but the entire presentation of the illness with nonspecific test results informs the experienced clinician of the diagnosis **(Müller et al., 2008)**.

Treatment varies according to the type and severity of the encephalopathy. Anticonvulsants may be prescribed to reduce or halt any seizures. Changes to diet and nutritional supplements may help some patients. In severe cases, dialysis or organ replacement surgery may be needed. Treating the underlying cause of the disorder may improve or reverse symptoms. However, in some cases, the encephalopathy may cause permanent structural changes and irreversible damage to the brain. Some encephalopathies can be fatal **(Müller et al., 2008)**.

Aim of the work

The purpose of this study is to discuss pathophysiology, diagnosis and management of encephalopathy in intensive care unit.

Anatomy and Physiology of brain circulation

All arterial blood supply to the brain and brainstem traverses branches of either the internal carotid or vertebral arteries (figures 1, 2 and 3). These arteries, in turn, receive blood from major branches of the arch of the aorta: the internal carotid is a major division of the common carotid artery while the vertebral is derived from the subclavian artery **(Drake et al., 2005)**.

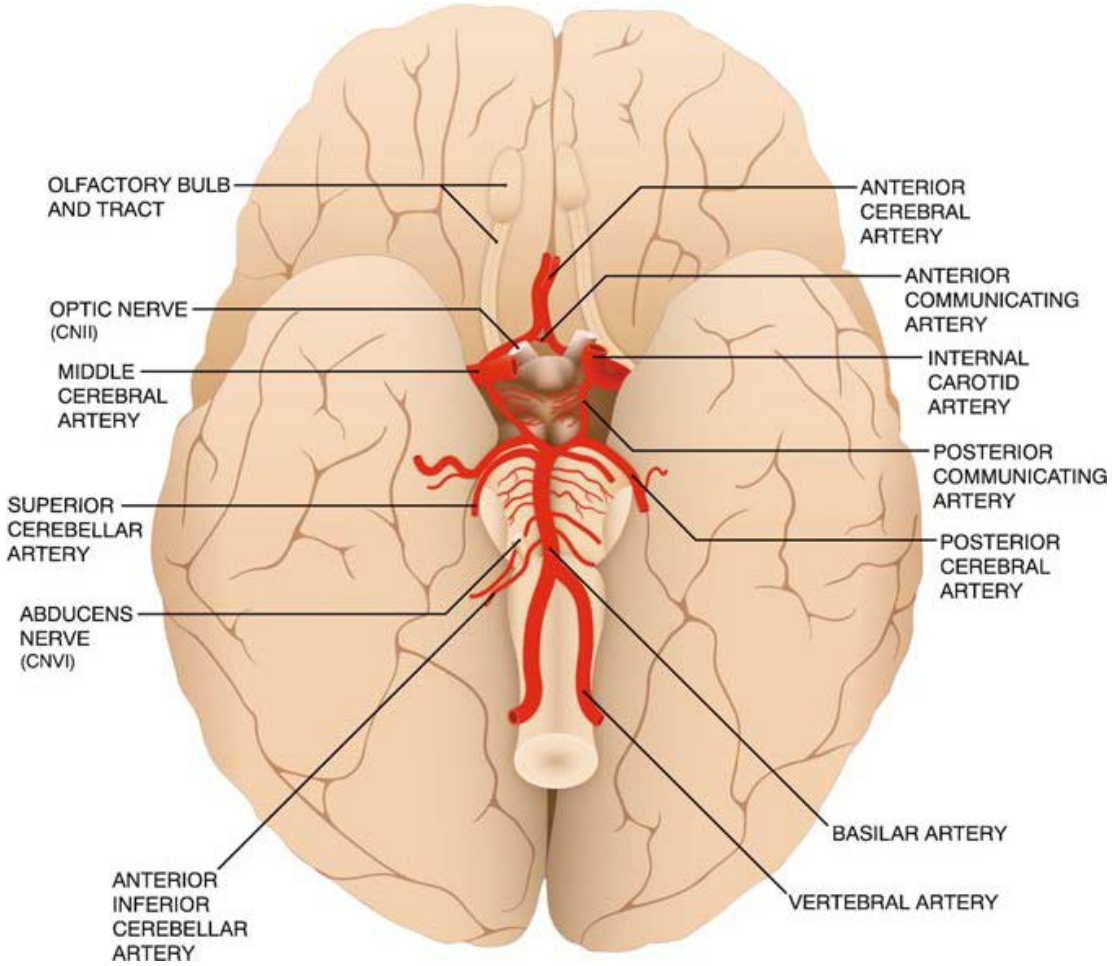

Figure (1): Vessels that contribute to the arterial circle of Willis at the base of the brain **(Drake et al., 2005)**

The blood supply to the brainstem, cerebellum, occipital lobe and the inferior aspect of the temporal lobe is derived from branches of the vertebral system. The frontal, parietal, upper 75% of the temporal lobes and the insular cortex receive their blood supply from the middle and anterior arteries, both of which are branches of the internal carotid system **(Desesso, 2009)**.

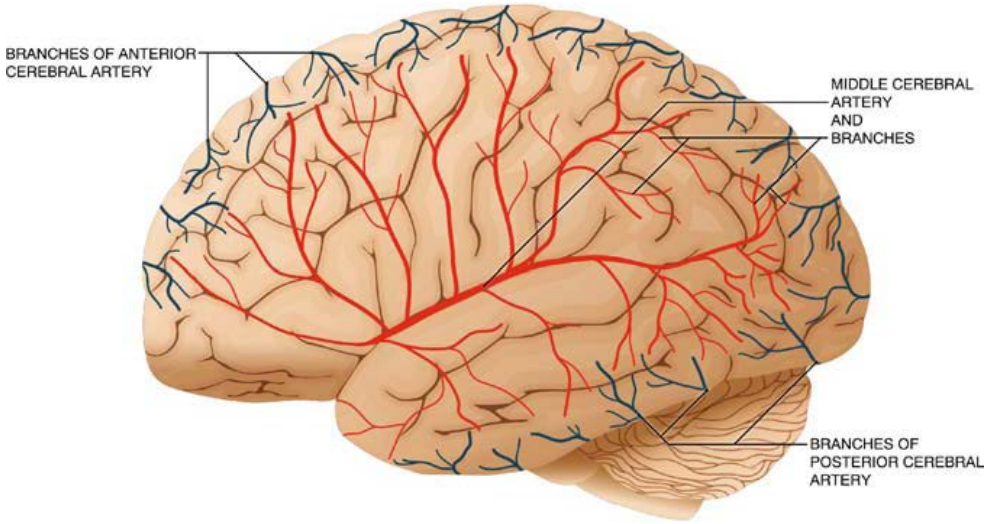

Figure (2): Distribution of blood supply to the lateral surface of the cerebrum **(Desesso, 2009)**

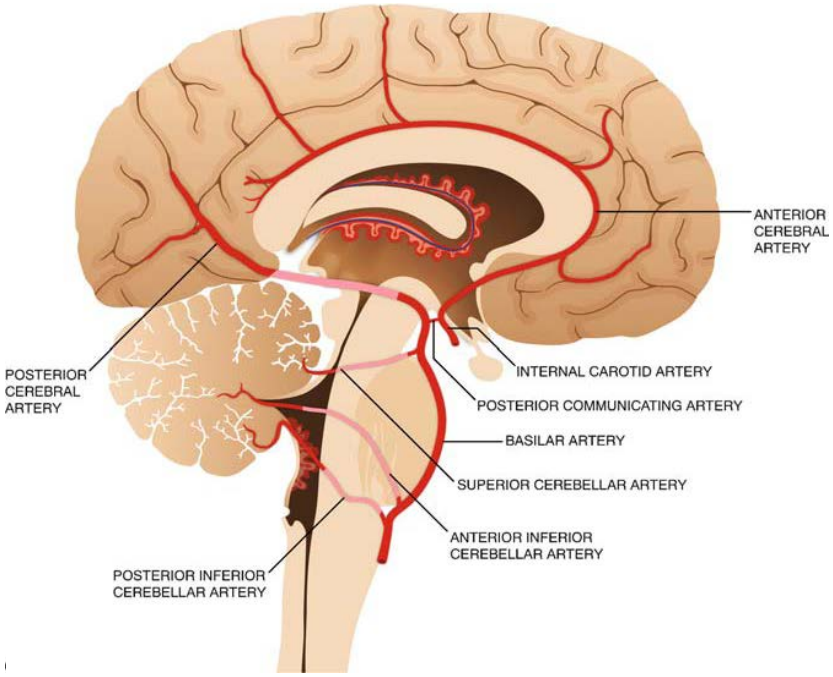

Figure (3): Sagittal section that depicts the distribution of blood flow to the cerebrum **(Drake et al., 2005)**

The basilar artery (derived from the fused vertebral arteries) terminates as the posterior cerebral arteries. The internal carotid arteries contribute the anterior and middle cerebral arteries and the posterior communicating arteries. The anastomosis is completed by the short anterior communicating artery between the two anterior cerebrals and the paired posterior communicating arteries between the posterior cerebral arteries and the middle cerebral artery. The latter arteries connect the vertebral and carotid blood supplies. Interestingly, the diameters of the arteries vary considerably, especially in the case of the posterior communicating arteries, which frequently may be extremely small on one side or even absent **(Drake et al., 2005)**.

The vertebral arteries branch from the subclavian arteries in the root of the neck and ascend within the foramina of the transverse processes of six of the cervical vertebrae (C_6-C_1). Upon exiting the transverse foramina of C_1, the vertebral arteries enter the skull through foramen magnum and approach each other in the midline where they fuse to form the basilar artery at approximately the level of the pontomedullary junction. The basilar artery travels rostrally in a groove on the base of the pons until it terminates as the superior cerebellar and posterior cerebral arteries **(Desesso, 2009)**.

Physiology of cerebral circulation:

In the brain, Cerebral Blood Flow (CBF) varies directly with cerebral perfusion pressure (CPP which is defined as the difference between mean arterial pressure and intracranial pressure) and inversely with cerebrovascular resistance (which is the sum of the resistance to flow generated by the vasculature, particularly at the level of the small pial arteries and penetrating pre-capillary

arterioles). In general, the contribution of any given cerebral vessel to overall CBF is defined by factors such as its radius and length, and the viscosity and pressure of blood flowing through it **(Werner, 1998)**.

The average rate of blood flow in the brain is approximately 50-55 ml/100 gm/minute. In pathological states, this global flow rate may decrease. The link between flow rate and electrophysiological and clinical findings underlies the concept of "flow thresholds". Remarkably, clinical evidence for a neurological deficit may not appear until average flow has fallen to 50% or below of normal levels (i.e. to approximately 25-30 ml/100 gm/min). At this threshold, global neurological impairment is noted and, below this, the margin between reversible and irreversible ischemic damage becomes narrow. Brain "electrical failure" begins at rates of about 16-18 ml/100 gm/min, while cytotoxic edema from failure of ionic pumps, particularly Na^+/K^+ATPases, develops at 10-12 ml/100 g/min. Finally, metabolic failure with gross disturbance of cellular energy homeostasis occur at rates of less than 10 ml/100 gm/min **(Friedman et al., 2005)**.

The incompressibility of the cranial vault mandated a relatively constant intracranial blood volume at all times. Any variation in the volume of one of the three principal intracranial contents, namely brain parenchyma (1200-1600 ml), blood (100-150 ml) and cerebrospinal fluid (CSF, 100-150 ml), was accompanied by a compensatory change in the volume of the other two. In fact, this latter notion forms the basis of the relationship between intracranial

pressure and cerebral blood volume (CBV). This pressure-volume relationship implies that in order to maintain a constant intracranial pressure in the face of rising CSF volume, blood volume must fall and when this can no longer occur, the brain will herniate caudally. Importantly, as intracranial pressure rises there is a fall in CBF in association with reduced CBV, most likely from structural compression of the vasculature **(Friedman et al., 2005)**.

Metabolism:

During resting conditions, approximately 15% of the cardiac output is directed to the brain to match cerebral oxygen consumption which is about 20% of the total body oxygen consumption. Due to the low energy storing capacity of the CNS, regulatory mechanisms are necessary to provide continuous substrate supply. There is a wide range of metabolic rates within the CNS tissues as resting CBF and metabolism are higher in cortical compared to subcortical tissues. The energetic requirements of the brain during activation are instantaneously met by increases in substrate delivery to the activated functional subunits (i.e. increases in CBF)

Cerebral vessels have sympathetic and parasympathetic innervation. Sympathetic fibres contain norepinephrine, ATP, and neuropeptide Y. The effects of cathecholamines on the cerebral circulation are diverse. Cathecholamines may increase or decrease both cerebrovascular resistance (CVR) and CBF. The individual response of the cerebral vasculature is related to the origin of the neurotransmitter **(Werner, 1998)**.

Autoregulation:

The term cerebral autoregulation (CA), coined by Lassen in 1959, describes the tendency of CBF to remain approximately constant when Mean Arterial blood Pressure (MAP) changes over a wide range, typically from 60 to 150 mmHg. CBF is relatively independent of CPP between the physiological limits of autoregulation, typically taken to be perfusion pressures of 50-60 mmHg for the lower limit and 150-160 mmHg for the upper. In normal subjects, CPP varies directly with MAP (due to constant ICP), varying directly with systolic blood pressure. Across the autoregulatory range of approximately 100 mmHg, in order to maintain a relatively constant CBF, cerebral arteries constrict as CPP rises and dilate as CPP falls. As a result, CPP and CBV are inversely related through this phenomenon **(Panerai et al., 2004)**.

The mechanism includes intrinsic changes in vascular smooth muscle tone (***myogenic hypothesis***) modulated by the release of a variety of vasoactive substances from the endothelium (***endothelial hypothesis***) and periadventitial nerves (***neurogenic hypothesis***) in response to changes in transmural pressure. A “metabolic” or “humoral” hypothesis has also been proposed to aid in the explanation of cerebral autoregulation. The description of metabolic regulation of cerebral vasomotor function rather than cerebral autoregulation is a pressure-dependent response, as follows:

- First, As measured by microdialysis, the extracellular and perivascular concentrations of H^+ and K^+ (key mediators in metabolic vasoregulation) normally do not change in response to CPP alterations in the autoregulatory range.

- Second, As reported in measuring changes in cerebroarterial diameter or tone in response to variations in perfusion or transmural pressure, autoregulation begins within a few seconds of the pressure change, and is typically complete within 15-30 seconds. Although not precluding their involvement in this process, this relatively rapid time course suggests that metabolic factors are less likely to be involved.
- Third, it has been reported that the brain's interstitial concentration of adenosine (another key mediator in metabolic hypothesis) may be increased at the lower limit of autoregulation **(Friedman et al., 2005)**

Despite the possibility of adenosine contributing to autoregulation at this extreme, its concentrations are known not to vary across the bulk of the autoregulatory range. Fourth, the autoregulatory response has been observed in isolated, perfused vessels in vitro (i.e. not subject to alterations in neuroglial metabolism), providing further evidence against a metabolic hypothesis. Taken together, metabolic factors, despite being capable of strong regulation of cerebral vasomotor function, are unlikely to play a major role in autoregulation **(Panerai et al., 2004)**.

Finally, it should be noted that there is increasing evidence that the myogenic response, classically thought of as the principal basis of cerebral autoregulation and an intrinsic property of vascular myocytes, is in fact modulated by endothelium-derived vasoactive substances such as nitric oxide, prostacyclin, endothelin-1 and thromboxane A_2, as well as perivascular nerve-derived vasoactive substances, including acetylcholine, nitric oxide, Calcitonin Gene-Related Peptide (CGRP), norepinephrine, serotonin, bradykinin and substance P **(Friedman et al, 2005)**.

Arterial gas tensions:

CO_2 is a potent modulator of CVR and CBF. Arterial hypercapnia dilates cerebral vessels, decreases CVR and increases CBF. In contrast, arterial hypocapnia constricts cerebral vessels, increases CVR, and decreases CBF. The changes in CBF during changes in $PaCO_2$ are associated with a non-linear change in cerebral blood volume. The dynamic changes in the diameter of the cerebral vessels occur at the level of the small cortical and tissue-penetrating arteries and arterioles. However, larger arteries are also involved in the regulation of CVR. Baseline arterioral tone is an important variable in the individual CBF response to changes in CO_2. As a consequence, the magnitude of cerebrovascular CO_2-reactivity may be modulated by the level of arterial blood pressure. Decreases in arterial blood pressure induce autoregulatory cerebrovascular dilation. In the presence of hypotension, any pre-existing autoregulatory decrease in cerebrovascular tone impairs the potential of cerebral vessels to further dilate with hypercapnia. Profound hyperventilation may decrease CBF below the ischaemic threshold. Although the major mechanism of cerebrovascular dilation is the decrease in perivascular pH induced by the increase in the tissue $PaCO_2$, Nitrous Oxide (NO) and cyclooxygenase pathways appear to be involved in this regulatory process **(Werner, 1998)**.

Pathophysiology of encephalopathy

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Risk factors:

Patients in an ICU are at high risk for encephalopathy because of:

- Multisystem illnesses and comorbidities.
- Use of psychoactive medications.
- Advanced age.
- Malnutrition.

(Aminoff, 2011)

Types:

There are many types of encephalopathy. Some examples include:

- **Mitochondrial encephalopathy:** Metabolic disorder is caused by dysfunction of mitochondrial DNA. It can affect many body systems, particularly the brain and nervous system.
- **Glycine encephalopathy:** A genetic metabolic disorder involving excess production of glycine.
- **Hepatic encephalopathy:** Arising from advanced cirrhosis of the liver.
- **Hypoxic ischemic encephalopathy:** Permanent or transitory encephalopathy arising from severely reduced oxygen delivery to the brain.
- **Static encephalopathy:** Unchanging, or permanent, brain damage.
- **Uremic encephalopathy:** Arising from high levels of toxins normally cleared by the kidneys; rare where dialysis is readily available.
- **Wernicke's encephalopathy:** Arising from thiamine deficiency, usually in the setting of alcoholism.
- **Hashimoto's encephalopathy:** Arising from an auto-immune disorder.
- **Hypertensive encephalopathy:** Arising from acutely increased blood pressure.
- **Chronic traumatic encephalopathy:** Progressive degenerative disease associated with multiple concussions and other forms of head injury.
- **Lyme encephalopathy:** Arising from Lyme disease bacteria, including Borrelia burgdorferi.

- **Toxic encephalopathy:** A form of encephalopathy caused by chemicals, often resulting in permanent brain damage.
- **Toxic-Metabolic encephalopathy:** A catch-all for brain dysfunction caused by infection, organ failure, or intoxication.
- **Transmissible spongiform encephalopathy:** A collection of diseases all caused by prions, and characterized by "spongy" brain tissue (riddled with holes), impaired locomotion or coordination, and a 100% mortality rate. Includes bovine spongiform encephalopathy (mad cow disease), scrapie, and kuru among others.
- **Neonatal encephalopathy:** An obstetric form, often occurring due to lack of oxygen in bloodflow to brain-tissue of the fetus during labour or delivery.
- **Salmonella encephalopathy:** A form of encephalopathy caused by food poisoning (especially out of peanuts and rotten meat) often resulting in permanent brain damage and nervous system disorders.
- **Encephalomyopathy:** A combination of encephalopathy and myopathy. It causes may include mitochondrial disease or chronic hypophosphatemia, as may occur in cystinosis.

(Müller et al., 2008)

I- Hepatic encephalopathy:

Hepatic encephalopathy (HE) is a serious neuropsychiatric complication of both acute and chronic liver disease. this disease encompasses a broad range of neuro psychiatric abnormalities of varying severity: affected patients exhibit alterations in psychomotor, intellectual, cognitive, emotional, behavioral and fine motor functions. He can be classified as either ‘overt’ or ‘minimal’. Overt HE (oHE) is a syndrome of neurological and neuropsychiatric abnormalities that can be detected by bedside clinical tests. By contrast, patients with minimal HE

(mHE) present with normal mental and neurological status upon clinical examination but specific psychometric tests yield abnormal results. A classification system for HE disorders was devised by the working Party at the 1998 world Congress of Gastroenterology in vienna, austria (figure 4). This classification has helped to standardize the nomenclature used in HE diagnosis and research worldwide **(Ferenci et al., 2002)**.

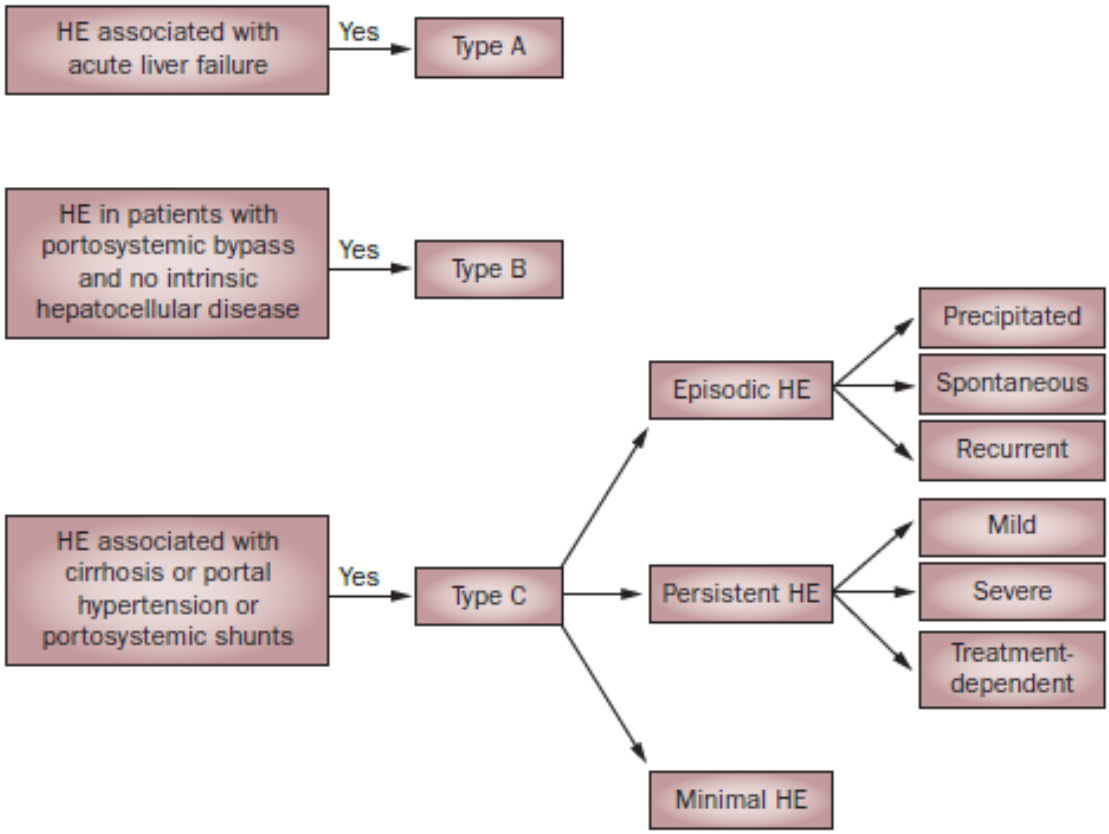

Figure (4): Classification of hepatic encephalopathy (HE) proposed by the Working Party at the 1998 World Congress of Gastroenterology, vienna, Austria. The Working Party proposed a classification system for HE to standardize the nomenclature used in HE diagnosis. HE can be graded into three types: Type A HE is associated with acute liver failure; type B HE is found in patients with portosystemic bypass and no intrinsic hepatocellular disease; type C HE is associated with cirrhosis or portal hypertension or portosystemic shunts. Type C HE can be further divided into three categories: episodic HE (precipitated; spontaneous; recurrent); persistent HE (mild; severe; treatment-dependent); minimal HE.