Neurochemistry International 60 (2012) 684–689

Contents lists available at SciVerse ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

Review

Reprint of: Neuroimaging in acute liver failure ☆

Laia Chavarria [a,b,c], Juli Alonso [c,d], Alex Rovira [d], Juan Córdoba [a,b,c,*]

[a] Servei de Medicina Interna-Hepatologia, Hospital Vall d'Hebron, Vall d'Hebron Institut of Research (VHIR), Barcelona, Spain
[b] Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain
[c] Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain
[d] Servei de Ressonància Magnètica (Institut de Diagnòstic per la Imatge), Departament de Radiologia, Hospital Vall d'Hebron, Barcelona, Spain

ARTICLE INFO

Article history:
Available online 12 April 2012

Keywords:
Hepatic encephalopathy
Magnetic resonance
Acute liver failure

ABSTRACT

Acute liver failure (ALF) is frequently complicated by the development of brain edema that can lead to intracranial hypertension and severe brain injury. Neuroimaging techniques allow a none-invasive assessment of brain tissue and cerebral hemodynamics by means of transcranial Doppler ultrasonography, magnetic resonance and nuclear imaging with radioligands. These methods have been very helpful to unravel the pathogenesis of this process and have been applied to patients and experimental models. They allow monitoring the outcome of patients with ALF and neurological manifestations. The increase in brain water can be detected by observing changes in brain volume and disturbances in diffusion weighted imaging. Neurometabolic changes are detected by magnetic resonance spectroscopy, which provides a pattern of abnormalities characterized by an increase in glutamine and a decrease in *myo*-inositol. Disturbances in cerebral blood flow are depicted by SPECT or PET and can be monitored and the bedside by assessing the characteristics of the waveform provided by transcranial Doppler ultrasonography. Neuroimaging methods, which are rapidly evolving, will undoubtedly lead to future diagnostic and therapeutic progress that could be very helpful for patients with ALF.

1. Introduction

The development of new technologies that allow in vivo assessment of brain morphology and function have been crucial for a better understanding of the pathogenesis of a variety of neurological disorders. These methods include microscopic information using techniques such as confocal microscopy or biophotonic imaging; as well as morphological, physiological and functional information using transcranial Doppler (TCD), computed axial tomography (CT) or magnetic resonance (MR) or images provided by radioligands detected by positron emission tomography (PET) or single photon emission computed tomography (SPECT). These methods are being progressively applied to investigate brain disturbances in acute liver failure (ALF). Most of the data currently originate of experimental models, which have benefit from the increasing availability of imaging resources for small animals. Studies in patients with ALF are scarce, because these patients are commonly in a critical condition, where neuroimaging investigations are difficult to perform. Extrapolation of the results in chronic liver failure patients with acute HE have been very helpful.

In this article we will review the data provided by different neuroimaging methods in patients and experimental models of ALF. Some data are controversial and have not been widely reproduced; differences among experimental models may explain part of the divergences. In spite of these caveats, the findings are discussed in relation to our current understanding of brain disturbances in ALF and how they may be helpful for future developments in the field.

2. Neuroimaging methods

2.1. Computed tomography (CT)

This a clinical fast technique that offers high-resolution images giving anatomical information related to bones, soft tissue and blood vessels to identify global abnormalities, in addition to

Abbreviations: ACLF, acute-on-chronic liver failure; ADC, apparent diffusion coefficient; ALF, acute liver failure; BBB, blood-brain-barrier; CBF, cerebral blood flow; Cho, choline compounds; CLF, chronic liver failure; CPP, cerbral perfusion pressure; Cr, creatine compounds; CT, computed tomography; FA, fractional anisotropy; Glx, glutamate and glutamine; HE, hepatic encephalopathy; ICP, intracranial pressure; MD, mean diffusivity; mIns, myo-inositol; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; PET, positron emission tomography; SPECT, single photon emission computed tomography; TCD, transcranial Doppler.

☆ A publisher's error resulted in this article appearing in the wrong issue. The article is reprinted here for the reader's convenience and for the continuity of the special issue. For citation purposes, please use the original publication details: Neurochemistry International, 59/8, pp. 1175–1180. DOI of original item: http://dx.doi.org/10.1016/j.neuint.2011.09.003.

* Corresponding author at: Servei de Medicina Interna-Hepatologia, Hospital Vall d'Hebron, Paseo Vall d'Hebron 119, Barcelona 08035, Spain.

E-mail addresses: laia.chavarria@vhir.org (L. Chavarria), juli.alonso@idi-cat.org (J. Alonso), alex.rovira@idi-cat.org (A. Rovira), jcordoba@vhebron.net (J. Córdoba).

0197-0186/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neuint.2012.03.015

outlining of organs or tumors with the administration of iodized contrast agents. The major value of CT is that is easy available and is a fast method to investigate changes in brain structure. During the procedure, it is possible to monitor the clinical status of the patient, better than during MR. For these reasons, CT is very useful for the diagnosis of intracranial complications, such as cerebral bleeding or cerebral herniation (Kumamoto et al., 2009). However, CT is less sensitive than MR to detect mild to moderate brain edema and does not allow the performing of additional techniques to investigate biochemical or functional abnormalities.

2.2. Magnetic resonance (MR)

MR is based on a property of the nuclei of certain atoms (most usual isotopes are ^{1}H, ^{31}P, ^{23}Na, ^{13}C), which absorb the energy at a selective radiofrequency under very powerful magnetic fields. Release of this excess of energy induces an electrical signal that, properly processed, will yield an image (magnetic resonance imaging, MRI) or a spectrum that enables metabolic analysis of a tissue (magnetic resonance spectroscopy, MRS). Since MR is sensitive to a high number of nuclei physicochemical properties, it is able to give interesting morphological and physiological information as well as in vivo metabolism. Morphological information is obtained mainly from T1-, proton density- and T2-weighted images.

Diffusion imaging is a variant of MRI that is sensitive to the restriction of local water diffusion. It offers quantitative information of water motion (apparent diffusion coefficient, ADC, or mean diffusivity, MD) and structural integrity (fractional anisotropy, FA). Diffusion studies are also capable of detecting damage to neuronal tracts, because the damage affects the diffusion of water along the axonal tracts. This damage is reflected in FA. Moreover, MR allows the assessment of changes in local blood flow and haemoglobin oxygenation by functional MRI and provides mapping of the functional centers of the human brain. In patients with chronic liver failure, MR has been applied in an important number of studies. One of the most characteristic findings is a high signal on T1-weighted images in the globus pallidus that can spread to other nuclei (Rovira et al., 2008) and has been attributed to manganese accumulation secondary to portal-systemic shunting (Rose et al., 1999). The process of manganese accumulation is slow and relates to the development of Parkinsonism (bradykinesia-rigidity). For this reason is usually not seen in ALF. However, one report describes high T1 signal and reversible Parkinsonism in one patient that developed ALF secondary to hepatitis E (Aggarwal et al., 2006).

MRS is an analytical technique to determine metabolic compounds of different biological tissues that is used to identify metabolic patterns of some disorders. Changes in the brain spectrum are typical from some disorders, such as hepatic encephalopathy (HE) (Kreis et al., 1992). Some of the metabolites of the spectrum that can be easily identified in the spectrum of healthy brain are N-acetylaspartate (NAA), glutamate and glutamine, creatine and phosphocreatine (Cr), choline-containing compounds (Cho), *myo*-inositol (mIns). However, it is important to note that glutamine (one of the metabolites implicated in ALF) shows a peak that cannot be separated easily from glutamate with the 1.5–3 Tesla MR systems. For this reason, glutamine and glutamate are usually grouped and referred as Glx. Several methods have been applied for quantifying the changes in the peaks of the spectrum; the most widely applied is the comparison of the peak of interest to the peak of creatine.

2.3. Nuclear imaging techniques

These techniques consist of assessing the signal generated by radioisotopes that are administered intravenously with PET or SPECT. The radioisotopes are linked to molecules, such as deoxyglucose, which allows following the metabolism of these compounds and obtain functional and metabolic information of the brain. The most relevant limitations are the spatial resolution that are capable to generate and the lack of information about the anatomical structures and the detected metabolic data.

PET gives quantitative data of isotope distribution (nCi/mL); the main isotopes used to study brain function are ^{15}O, ^{13}N, ^{11}C, and ^{18}F. In contrast, SPECT provides only relative measurements of the radioactivity (counts/mL) and uses uncommon biological elements such as ^{99}mTc. However, SPECT is more easily available and less expensive than PET. One recent application is bimodal imaging that combines the anatomical images of CT or MR with functional images of PET. Examples of the use of this methodology are the ^{13}N-ammonia PET studies that have been performed to investigate brain ammonia metabolism in cirrhosis. These studies have shown that intracellular metabolism of ammonia increases in patients with cirrhosis and overt HE, which is in accordance to the important role of ammonia in the pathogenesis of HE (Iversen et al., 2009). ^{13}N-ammonia PET studies have not been undertaken in patients with ALF.

2.4. Transcranial Doppler (TCD)

TCD is a noninvasive device which can continuously measure cerebral blood flow velocity (CBF), producing a velocity-time waveform that indirectly monitors changes in cerebral hemodynamics, including intracranial pressure (ICP). In addition, TCD avoids the risks of hemorrhage and infection that are associated with ICP monitors. Blood flow velocity is recorded by emitting a high-pitched sound wave from the ultrasound probe. The speed of the blood in relation to the probe causes a phase shift. TCD does not allow assessment of CBF, because the velocity of blood depends on the diameter of that vessel that is variable, but is useful to estimate relative changes in flow and has become part of the monitoring armamentarium in neurocritical units. By assessing the velocity–time waveform it is possible to indirectly monitor changes in cerebral hemodynamics, such as ICP and cerebral perfusion pressure (CPP). The waveform has two phases namely a systolic double peak and a diastolic depression. The morphology is affected by cerebral hypertension and parallel changes in CPP (Aggarwal et al., 2008).

2.5. The brain in acute liver failure

The hallmark of ALF is the development of a decrease in consciousness that is attributed to an insufficient liver function. This situation that is identified as HE is different from a series of disturbances that are common in ALF and that may impact directly on brain function, such as hypoglycemia or sepsis. The mechanisms that generate HE in ALF are in many ways similar to those present in chronic liver failure. Liver failure impairs several metabolic pathways and increases plasma levels of substances, such as ammonia, which is considered a key factor in HE. Other features of major pathophysiological importance are the activation of a systemic inflammatory response, circulatory dysfunction and failure of other organs that can cause directly disturbances to brain function. These disturbances induce brain edema, which has an important role in ALF, cause neurometabolic changes and impact on CBF and neuroenergetics.

2.6. Brain edema in ALF

Traditionally, intracranial hypertension secondary to brain edema was considered the main cause of death in ALF (Jalan et al., 2004). Improvements in the intensive care management of patients with ALF have been associated with a decrease in the frequency of this complication that nowadays is responsible of death in less than 25% of patients (Wendon et al., 2010). The increment of cerebral