Hepatic Encephalopathy: Historical Remarks

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The history of hepatic encephalopathy (HE) is briefly reviewed since the beginning of western medicine by Hippocrates. For about 2000 years the main evidence was the mere association between jaundice, fever and delirium. A clear link between delirium and cirrhosis was proven in the 17th century by Morgagni. In subsequent times the focus was mainly the descriptions of symptoms and the only pathophysiological improvement was the evidence that jaundice, *per se*, does not alter brain function. Only at the end of the 19th century Hann et al proved the role of portal-systemic shunt and of nitrogenous derivatives in the pathophysiology of the syndrome. A terrific development of knowledge occurred in the last 60 years, after the works of Sherlock in London. Nowadays some consensus about HE was reached, so that new developments will likely occur. (J CLIN EXP HEPATOL 2014;5:S4-S6)

The association between liver disease and mood disturbances was recognized, at least in the western world, by the father of medicine, Hippocrates (460–371 B.C.). More precisely, he described the association between jaundice and acute behavioral disturbances. It is reasonable, therefore, that he and his disciples may have observed encephalopathy associated with severe liver insufficiency (Figure 1).¹

In addition, the humoral theory, which was accepted as explicatory paradigm in western medicine till modern age, emphasized the relationship between bile and irritability. However, this convincement may simply have derived by the fact that the four humors, which in those times were considered to explain human physiology, had been associated to behavioral features. The Roman and medieval medicine, in Europe, did not produce significant improvements concerning the relationship between the liver and the brain, even if this linkage was emphasized by the Roman physician Galen.

It is necessary to wait till the 18th century to find a true description of the mental dysfunction that can occur in liver cirrhosis. This description was done by GB. Morgagni (1682–1771) – Professor of Theoretical Medicine in Padua, Italy – who described a case of hepatic encephalopathy in the 38th letter of the 3rd book of the treatise ‘*De sedibus et causis morborum per anatomen indagatis*’ (Figure 2a). He reported the history of a noble from Venice who was an alcohol misuser in the past. This man developed ascites and some episodes of agitation, and then he developed prolonged episodes of somnolence and delirium and finally

died. His autopsy revealed the existence of liver cirrhosis (the Morgagni-Laennec cirrhosis).² The existence of episodes of delirium, somnolence and coma in liver disease is clearly reported in the famous treatise on liver diseases by F.T. Frerichs,³ however generally related to acute jaundice, fever or acute liver atrophy (Figure 2b). However, the link between the brain and the liver remained elusive, even if a toxic effect of jaundice *per se* was excluded, as well as the existence of evident morphological brain abnormalities. Remarkable improvement in the description of the syndrome were negligible in subsequent years and the interest of the authors was mainly descriptive, as nicely reviewed by Whalsh.⁴

A clear improvement in the understanding of hepatic coma came from the experimental studies by Hann et al⁵ who showed that dogs undergoing experimental portal-caval shunt develop behavioral changes within 10–40 days after surgery. The symptoms include irritability, ataxia, convulsions, and coma. They worsen after a meat feed, but not after ingestion of milk or bread. Consequently, the authors called this disorder an ‘encephalitis’ related to a ‘meat intoxication syndrome’. In this way a great improvement was achieved to understand the relationship between the liver and the brain. The pathophysiology does not regard bile, but 1) a nitrogenous substance highly extracted by the liver, since porto-caval shunt greatly increases the concentration of substances having high liver extraction, 2) the quality of food intake has a relationship with behavioral alterations.

The capacity of ammonia to induce coma or stupor in patients with cirrhosis was clearly proven in humans in the thirties by van Coultet et al,⁶ in France, who administered oral ammonia salts loads, and by the comatogenous side effect of the first diuretics substances that increased ammonia level. Notably, since those times it was clear that the oral ammonia load capable to produce coma was not constant, and the same patient could or could

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Figure 1 The English version of the “Prognostic and Prorrhethics” by Hippocrates.

not develop coma with the same ammonia load, thus highlighting the concept that other factors interact with ammonia in causing hepatic coma.

A definite improvement in the description of the clinical findings, the pathophysiology and treatment of hepatic encephalopathy was given by S. Sherlock and her disciples in London.⁷ She also coined the term ‘portal-systemic encephalopathy’ that was exceptionally appropriate to underline that: 1) the symptoms are not only limited to coma, but to a wide spectrum of manifestations both behavioral and neurological, 2) the symptoms are ascribable to an underlying dysfunction of the brain and, consequently, this dysfunction is relevant for clinical investigation, 3) portal-systemic shunt, and therefore substances of gut origin with high hepatic extraction, are key element in the pathophysiology of the disorder. In addition, she confirmed the relevant role of hyperammonaemia in the pathophysiology of the disorder and the role of gut microbiota that could be modulated by antibiotics to revert coma. Notably, the first antibiotics that were proved to be useful were tetracyclines and not non-absorbable antibiotics.

With Sherlock and, before of her, with Hann and Coult, the mere syndromic association between neurological/

(a)

(b)

Figure 2 The Treatises by Morgagni (a) and the English version of the one by Frerichs (b).

mental disorders and liver insufficiency, which has been observed since the beginning of medicine history, began to become a real disease, with at least some clear pathophysiological mechanisms and the ensuing rational treatment.

Another great contribution to the notion of ‘encephalopathy’ that overtake the concept of a mere association of behavioral symptoms with liver disease derived by the neurophysiologic studies on the alteration of brain electrogenesis that were found not only in individuals with hepatic coma,⁸ but also in individuals with mild or even no behavioral manifestations of the disease.⁹

The new term ‘hepatic encephalopathy’ (HE) was coined, at my knowledge, by Fazekas, et al¹⁰ and this term further extended the concept to the encephalopathy in which the role of shunt is negligible -or absolutely absent-, such as the one of acute liver failure.

A new step forward in the knowledge of HE was done by Rikkers et al¹¹ who recognized the existence of a latent condition of HE in which, despite the absence of evident symptoms, the patient displays cognitive abnormalities on psychometrical examination or neurophysiologic alterations on the EEG. Notably, the finding that about 40% of inpatients with cirrhosis have an abnormal EEG was detected in the fifties by Parsons-Smith et al⁹ in London, but they did not recognize the importance of their findings. This latent condition of HE was later termed minimal HE (MHE),¹² worrying that the term ‘subclinical’ might induce the false idea that this condition is trivial and without clinical implications.¹³

Since those times, the items concerning HE are more ‘news’ than ‘history’. In brief, insight was provided concerning i) the brain alterations, which have been studied with new technologies, ii) the clinical picture, iii) the prognostic/clinical implications and therapeutic options.

In these last years, for the first time, important consensus was reached both concerning the definition of HE, the main practical issues about HE,¹⁴ and its nutritional management,¹⁵ thus providing an important ground for further developments.

CONFLICTS OF INTEREST

The author has none to declare.

REFERENCES

1. Moffat J. *Prognostics and Prorrhetics of Hippocrates Translated from the Original Greek*. London (UK): Bensley; 1788.
2. Morgagni GB. *De sedibus et causis morborum per anatomen indagatis*. Venice: Typographia Remondiniana; 1761.
3. Murchinson C. *Translation of the Clinical Traetise on Diseases of the Liver by Ferrius F.T*. London: The New Sydenham Society; 1860.
4. Walshe JM. Observations on the symptomatology and pathogenesis of hepatic coma. *Q J Med*. 1951;20:421–438.
5. Hahn M, Massen O, Nencki M, Pavlov I. Die Eck'sche fistel zwischen der unteren hohlvene und der pfortader und ihre folgen fur den organismus. *Arch Exp Pathol Pharm*. 1893;32:161–210.
6. Van Caulert C, Deviller C, Halff M. Troubles provoques par l'ingestion de sels ammoniacaux chez l'homme atteint de cirrhose de Laennec. *Comptes Rendus Soc Biol*. 1932;111:739–740.
7. Sherlock S, Summerskill WHJ, White LP, Phear EA. Portal-systemic encephalopathy. Neurological complications of liver disease. *Lancet*. 1954;267:453–457.
8. Adams RD, Foley JM. The neurological disorder associated with liver disease. *Res Publ Assm Res Nerv Ment Dis*. 1953;32:198–237.
9. Parsons-Smith BG, Summerskill WHJ, Dawson AM, Sherlock S. The electroencephalograph in liver disease. *Lancet*. 1957;273:867–871.
10. Fazekas JE, Ticktin HE, Shea JG. Effects of L-Arginine on hepatic encephalopathy. *Am J Med Sci*. 1957;234:462–467.
11. Rikkers L, Jenko P, Rudman D, Freides D. Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. *Gastroenterology*. 1978;75:462–469.
12. Schomerus H, Hamster W. Neuropsychological aspects of portal-systemic encephalopathy. *Metab Brain Dis*. 1998;13:361–377.
13. Lockwood AH. “What's in a name?” Improving the care of cirrhotics. *J Hepatol*. 2000;32:859–861.
14. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. 2014;60:715–735.
15. Amodio P, Bemeur C, Butterworth R, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. *Hepatology*. 2013;58:325–336.