Chapter 11

Metal Toxicity and Brain–Liver Axis: The Good, the Bad, and the Neurodegenerated

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ABSTRACT

The liver is the main detoxifier organ of the body. When normal liver function is compromised, other systems in the body can be affected, including the brain. Hepatocerebral disorder is the term used to describe some neuropsychiatric conditions that result from liver failure and characterized by the accumulation of these toxic metals in brain. Examples of such disorders are Wilson’s disease (WD), an autosomal recessive disorder that is characterized by the deposition of copper in liver and brain tissues and acquired (non-Wilsonian) hepatocerebral degeneration (AHCD), a complication that occurs most frequently in patients with hepatic coma or that suffered multiple episodes of severe HE. AHCD is characterized by accumulation in brain of manganese. This chapter will focus on the crucial importance of relationship between liver and brain functioning and on the effects produced when this relationship is compromised. Specifically, the chapter will discuss on the physiopathology of WD and AHCD and on the role that toxic metals play on neurological symptoms in such disorders.

LIVER-BRAIN AXIS: FROM BABYLONIANS TO OUR DAYS

The liver is the main detoxifier organ of the body. When normal liver function is compromised, also other systems in the body can be affected, including the brain. This makes the relationship between the liver and the brain very important and the normal brain functioning depends on normal liver functioning.
This relationship was already known more than 4000 years ago, when the Babylonians attributed powers of augury and divination to the liver, designating it by the term used also for ‘soul’ or ‘mood’ (Davidson & Summerskill, 1956).

Nearly 2500 years ago, Hippocrates (460-377 B.C.) was the first to make an association between hepatic disease and impaired brain function. In fact, the Father of Medicine observed that “Those who are mad on account of phlegm are quiet, but those on account of bile are vociferous, vicious, and do not keep quiet” (Summerskill, Davidson, Sherlock, & Steiner, 1956). This was the beginning of humoral medicine, developed by Hippocrates and consisting in four humors: 1) the blood with its warm and wet properties corresponded to air; 2) warm and dry yellow bile corresponds to fire; 3) cold and dry black bile to soil and 4) the phlegm with its cold and wet properties corresponds to water. (Nam, 2014). According to this theory, the human healthy depended on the balance and harmony of these four elements.

This belief dominated medical practice for many centuries, from Greek to Romans. In fact, Galen (A.D. 131-200) a Greek physician and Celsius, a Greek philosopher (c. A.D. 30) also attributed the influence of liver function on personality, behaviour, and physical infirmity (Summerskill et al., 1956).

With the fall of the Roman Empire, also the status of the liver declined from that of a ‘vital organ’ to a ‘great, bile producer’. Only in the 18th century, the relationship between hepatic function and neuropsychiatric disorder was emphasized again and new definition of ‘hepatic coma’ was elaborated to include an immense variety of clinical features. This definition was created by Gianbattista Morgagni, a professor of Theoretical Medicine in Padua. Morgagni described an initial phase observed in his patients where they appear stupid, forgetful and suffered from a ‘suppression of the senses’, later followed by violent delirium, progressing to terminal coma (Morgagni, 1820).

At the end of the 20th century, the interdependence of liver and brain functioning was finally demonstrated by Marcel Nencki and Ivan Pavlov. They described the physiological consequences of a portacaval shunt (PCS) in dogs, a surgical procedure still used today in rats to reproduce hepatic encephalopathy and first described by Eck in 1879 (“Eck’s fistula”) (Starzl, PORTER, & FRANCAVILLA, 1983). Such dogs developed neurobehavioral changes in 10 days to 6 weeks postsurgery; symptoms included aggression, irritability, ataxia, convulsions, and coma (Hahn, Massen, Nencki, & Pawlow, 1893).

Today, the main role of liver as detoxifier organ and its interconnection with brain functioning is well studied. The liver cleanses the blood of substances, which if not eliminated, could penetrate the blood-brain-barrier and damage the brain cells. These substances which include many metals such as copper, manganese, and iron are responsible of some conditions known as hepatocerebral disorders. Examples of such disorders are: Wilson’s disease (WD), Acquired (non-Wilsonian) hepatocerebral degeneration (AHCD) and Hepatic encephalopathy (HE).

**ACQUIRED HEPATOCEREBRAL DEGENERATION: STORY AND PHYSIOPATHOLOGY OF A RARE NEUROPSYCHIATRIC SYNDROME**

Acquired hepatocerebral degeneration (AHCD) is a brain disorder that occurs in people with liver damage. Its symptomatology is often confused with that observed in patients with hepatic encephalopathy or Wilson’s disease. AHCD was first described by Van Woerkom in 1914 but only 50 years after, Victor and coworkers realized the first and complete anatomopathological description of disease (Victor, Adams, & Cole, 1965). With their work, Victor et al., fundamentally distinguished AHCD from Wilson’s disease. Neuropathological findings included patchy cortical laminar neuronal loss, neuronal drop-out...
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