SLEEP DISORDERS AND PORTAL–SYSTEMIC ENCEPHALOPATHY FOLLOWING TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT SHUNT IN PATIENTS WITH LIVER CIRRHOSIS

Relation to Plasma Tryptophan

J. Wiltfang¹, W. Nolte², J. von Heppe¹, E. Bahn¹, J. Pilz¹, G. Hajak¹, E. Rüther¹, and G. Ramadori²

Neurobiological Laboratory, Dept. of Psychiatry¹ and Dept. of Internal Medicine²
Division Gastroenterology and Endocrinology
University of Göttingen
von-Siebold-Str. 5, D-37075 Göttingen
Germany
Phone: +49-551-39-9794
Fax: +49-551-39-2241
e-mail: jwiltfa@gwdg.de

ABSTRACT

Neuropsychiatric symptoms due to any type of dysfunction and/or portal-systemic shunting are summarized as hepatic encephalopathy (HE). HE in the presence of liver cirrhosis and/or portal-systemic shunting has been termed portal-systemic encephalopathy (PSE). PSE is most frequent among the HE syndromes and is almost exclusively seen in patients with advanced cirrhosis and portal hypertension. Portal-systemic shunting either spontaneous due to portal hypertension, following surgical portocaval anastomosis, or subsequent to transjugular intrahepatic portosystemic stent-shunt (TIPSS) is regarded as the primary causative condition for PSE, not hepatic dysfunction per se. PSE may be considered as a disorder of multiple neurotransmitter systems among which derangements of the serotonergic system have been documented most consistently. Incipient PSE is frequently paralleled by the occurrence of sleep disorders, however, their relation to PSE remains unclear. We observed a transient increase of sleep disorders post-TIPSS, which were only in part correlated to other symptoms of PSE. Among the biochemical parameters studied only an association between arterial ammonia levels and sleep disorders became apparent, whereas no significant relation was observed for peripheral tryptophan.
1. INTRODUCTION

Neuropsychiatric symptoms due to any type of hepatic dysfunction and/or portal-systemic shunting are summarized as HE, which includes a number of discrete syndromes (Conn and Lieberthal, 1978). Thus the latter diagnosis comprises acute HE following fulminant hepatic failure, as well as HE in the presence of liver cirrhosis and/or portal-systemic shunting, which has been termed portal-systemic encephalopathy (PSE) (Sherlock et al., 1954). PSE is most common of the HE syndromes and is almost exclusively seen in patients with advanced cirrhosis and portal hypertension. Portal-systemic shunting, either spontaneous due to portal hypertension, following surgical portocaval anastomosis, or subsequent to transjugular intrahepatic portal-systemic stent-shunt (TIPSS) (Rössle et al., 1998), is regarded as the primary causative condition for PSE, and not hepatic dysfunction per se. Correspondingly, resection of pancreatic neoplasms with concomitant portal-systemic shunting or spontaneous portal-systemic collaterals in noncirrhotic patients with normal liver function may induce PSE (Ohnishi et al., 1985).

Besides clinically overt PSE, a condition called latent or subclinical PSE (sPSE) can be defined which is characterized by the presence of one or more quantifiable neuropsychologic or electrophysiologic abnormalities (Conn, 1977; Schomerus et al., 1981; Weissenborn et al., 1998). The incidence of overt or subclinical PSE in patients is increased to 30–50% (range: 4–80%) and 30–40% (range: 3–75%) following surgical portocaval anastomosis (Sarfeh et al., 1983; Planas et al., 1992; Paquet et al., 1995) and TIPSS (Sanyal et al., 1994; Jalan et al., 1995; Somberg et al., 1995; Jabbour et al., 1996; Pomier-Layrargues, 1996; Rössle et al., 1997; Nolte et al., in press), respectively. The pathophysiology underlying PSE has yet to be resolved, but it may be considered as a disorder of multiple neurotransmitter systems (Butterworth, 1997), since glutamatergic, monoaminergic, and GABAergic neurotransmission seem to be involved (Basile and Jones, 1997; Bengtsson et al., 1997; Jones and Weissenborn, 1997). The latter derangements appear to be related to the intracerebral accumulation of neuroactive or neurotoxic substances like ammonia, tryptophan and metabolites, manganese or endogenous compounds with an affinity to the GABA-related benzodiazepine receptor.

Typically PSE develops slowly, affecting very heterogeneous levels of mental functions at the same time. The further course is characterized by significant fluctuations of the symptoms, which may remit and recur within a single day. PSE is reversible and responds to treatment with lactulose, lactitol, neomycin, protein-restricted diet and the careful maintenance of energy, fluid and electrolyte balance.

Initially sleep disorders like insomnia, hypersomnia, or inversion of sleep patterns, discrete cognitive impairments, mood disorders with usually mild depressive or hypomanic features, and changes in personality become apparent. Concomitant neurological abnormalities are documented as tremor, incoordination, impaired hand-writing and discrete constructional apraxia. Deficits of memory functions usually are clinically not overt, but, may be verified by psychometric testing.

Sleep disturbances in patients with liver cirrhosis are generally regarded as a symptom indicating early PSE, but, systematic studies are rare (Tarter et al., 1984; Quero et al., 1995). Only recently it was recognized that disturbances of sleep in those patients may present as a unique diagnostic entity, i.e. occurring independently of other symptoms, indicating clinically overt or subclinical PSE (Wiltfang et al., 1996; Cordoba et al., 1998). Derangements of serotonergic neurotransmission may be central to the pathophysiology of sleep disorders indicating early PSE.