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Neurological and neuropsychiatric comorbidities occurring in fatty liver diseases

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Introduction: The most common liver diseases associated with the fat accumulation in the hepatic tissue are metabolic associated fatty liver disease (MAFLD), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). Many studies previously reported several key mechanisms tying hepatic injury to extrahepatic manifestations. In this way, the co-occurrence of cognitive decline, mood, and affective changes could suggest the existence of a strong neurological component predisposing to neuropsychiatric comorbidities.

Objectives: In this study, we aimed to describe the neurological and neuropsychiatric comorbidities of MAFLD, NAFLD, and NASH.

Methods: The main scientific databases were screened for English-written studies using the following key words: “cognitive decline”, “neuronal loss”, “affective disorders”, “anxiety”, “depression”, “MAFLD”, “NAFLD”, “NASH”. Exclusion criteria: (1) studies not focussing on fatty liver diseases; (2) not describing comorbid conditions; (3) not providing correlative analysis of disease co-occurrence or mechanistic associations.

Results: Hepatic encephalopathy (HE) is the main NAFLD/NASH extrahepatic manifestation commonly characterized by impaired cognition, rapid mood swings, depressive and anxious behaviours, and defective sleep. It is currently reported that more than 70% of the cirrhotic patients develop HE. Cognitive impairments and brain tissue reduction were found in NAFLD patients, while MAFLD patients’ cognitive dysfunctions (mild cognitive impairment and hippocampal-dependent memory impairment) were not associated with the presence of metabolic syndrome. Similarly Alzheimer’s disease (AD) was not described as comorbid in MAFLD. By contrast, since NAFLD and NASH are often characterized by insulin resistance and dyslipidaemia – significant triggers of dementia. By far the most prevalent neuropsychiatric comorbidity in NAFLD and NASH is the major depressive syndrome, diagnosed in almost 30% of the cases. Also, a correlation between the anxiety manifestation and the progression from NAFLD to NASH was described. In this context, as a response to the vast evidence that connect liver dysfunction to cognitive impairments, the liver-brain axis function was hypothesized.

Conclusions: MAFLD, NAFLD, and NASH are frequently associated with cognitive decline. The main NASH neurological comorbidity is hepatic encephalopathy, but it could also be seen in NAFLD. While Alzheimer’s disease occurs in NAFLD and NASH, more studies are needed to explain the severity-dependent association. Depression and anxiety were also reported in NAFLD and NASH.

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Tobacco and mental health: Deciphering the vulnerability to nicotine in patients with schizophrenia as a function of their dopamine neurotransmission genes: a clinical and preclinical study

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Introduction: Schizophrenia (SZ) is a severe and frequent mental disorder that has multifactorial origins (genetic but also environmental vulnerability, gene environment interactions). Our team has shown that in France smoking is common among these patients and often begins before the onset of symptoms. This calls into question the hypothesis of self-medication of psychotic symptoms and cognitive disorders by tobacco consumption, and raises the question of specific interactions between nicotine consumption and the genes of the dopaminergic and cholinergic nicotinic systems, in particular with regard to adolescence, period of neurodevelopmental vulnerability.

Objectives: to study (i) the interactions between the DA system and exogenous nicotine in a pre-clinical mouse model (transgenic for DAT) (ii) the impact of smoking on the psychotic and clinical phenotype in a national cohort of SZ patients (iii) interactions between tobacco consumption and several genetic polymorphisms of the dopaminergic and nicotinic system in SZ population.

Hypothesis: Disruption of the balance between DA and nicotine systems by nicotine consumption in adolescence may be a key neurobiological mechanism for the emergence of SZ disorders.

Methods: The characterization of the model is behavioral (anxiety, memory, social interactions, locomotion, motor coordination) but also biochemical. For the clinical approach, we exploit the clinical / cognitive / genetic data of a national cohort (Fundamental foundation) and another smaller and local cohort.

Results: We demonstrate, for the clinical study, that some clinical and cognitive characteristics are associated with tobacco use in schizophrenia patients, with more cognitive disturbances in smokers, against the self medication hypothesis. Genes environment interactions also demonstrate associations with genes involved in dopaminergic system. Regarding the preclinical study, we show a gene environment interaction, as heterozygote mice for the DAT