Cognitive Dysfunction in NAFLD

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Non-alcoholic fatty liver disease (NAFLD) has emerged as the hepatic component of the metabolic syndrome and now seemingly affects one-fourth of the world population. Several features associated with NAFLD have frequently been linked to cognitive dysfunction, i.e. systemic inflammation, impaired urea synthesis, vascular dysfunction, gut dysbiosis, and sleep apnoea. Considering the growing burden of NAFLD, the morbidity from cognitive dysfunction is expected to have huge societal and economic impact. Here, a review of the clinical evidence of cognitive dysfunction in NAFLD is provided.

non-alcoholic steatohepatitis cognition inflammation ammonia vascular dysfunction neuro-degeneration neuropsychology psychometric hepatic encephalopathy.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the hepatic component associated with the metabolic syndrome and constitutes a major global health burden, affecting an alarming one-fourth of the general population worldwide [1][2][3]. NAFLD comprises the progressive disease spectrum from simple steatosis through non-alcoholic steatohepatitis (NASH), with or without fibrosis, to cirrhosis [4][5][6][7]. Morbidity and mortality are related to both the liver disease itself and to extrahepatic complications associated with NAFLD and the metabolic syndrome, in particular cardiovascular disease [8][9][10][11][12][13]. In recent years, also cognitive dysfunction has been increasingly recognized as a complication of NAFLD [14][15] as problems with memory, attention, concentration, forgetfulness, and confusion have been reported in up to 70% of NAFLD cases with associated negative impact on everyday living and quality of life [16][17][18][19]

The metabolic syndrome is defined by the presence of abdominal obesity, peripheral insulin resistance, hypertension and dyslipidaemia [20]. Several features of the metabolic syndrome, i.e., systemic inflammation, vascular dysfunction, atherosclerosis and obstructive sleep apnoea (OSA), have frequently been linked to cognitive disturbances, which has given rise to the concept of the metabolic cognitive syndrome [21]. These are all features also linked with NAFLD [22][23], but it is unclear if NAFLD in itself gives rise to and contributes to cognitive dysfunction. Adding to these features, NAFLD exhibits disruption of the gut microbiota and impairment of urea synthesis in the liver, leading to ammonia accumulation even in precirrhotic stages [24][25]. These disturbances, compounded by systemic inflammation, are central elements of the gut–liver–brain axis and acknowledged as significant in the pathogenesis of hepatic encephalopathy (HE), the neuropsychiatric syndrome associated with progressive liver injury [26][27][28][29].

Considering the high prevalence of NAFLD, its potential adverse impact on cognitive function represents a clinical challenge with expected huge societal and economic consequences. Underneath, a review of the clinical evidence of cognitive dysfunction in NAFLD is provided.

2. Evidence for Cognitive Dysfunction in NAFLD

The existing literature on cognitive dysfunction in NAFLD is outlined in Table 1. Cognitive function in NAFLD has only been investigated on a larger scale in three population-based observational studies. The first comprehensive study was undertaken by Seo et al. using data from the 1988–1994 National Health and Nutrition Examination Survey (NHANES), comprising 874 NAFLD patients and 3598 healthy controls below the age of 59 years [30]. Here, NAFLD was associated with poor memory and attention (serial digit learning task; SDLT), independent of important confounders. In addition, NAFLD patients showed deficits in visuospatial function (digit symbol substitution test; DSST) and psychomotor speed (simple reaction time test; SRTT). However, the latter deficits were not significant after adjustment for life-style related confounders. Weinstein et al. (2018) used NHANES data from 2011 to 2014, comprising 1102 subjects above 60 years of age whereof 413 were diagnosed with NAFLD [31]. In this study, a lone NAFLD diagnosis was not associated with poor performance on any of the cognitive tests, whereas NAFLD with concurrent type 2 diabetes mellitus (T2DM) was associated with impaired visuospatial function (DSST). In fact, this group performed significantly worse than all other groups, including T2DM alone, suggesting that NAFLD adds to the cognitive dysfunction in T2DM that has frequently been reported [32] Finally, Weinstein et al. (2019) studied cognitive function in 1278 subjects of which 378 had a NAFLD diagnosis, using data from the Framingham Heart Study [33]. Overall, NAFLD was not independently associated with cognitive dysfunction. However, a subgroup of NAFLD patients with high risk of having hepatic fibrosis (measured as the NAFLD fibrosis score (NFS)) exhibited signs of impaired executive function (Trailmaking A–B) and abstract reasoning (Wechsler adult intelligence tests-revised (WAIS-R) similarities test; SIM), compared to those with low risk. Smaller cross-sectional studies have found that patients with NAFLD underperform when tested with general dementia screening tools such as the mini mental state examination (MMSE) and Montreal cognitive assessment (MoCA), however, most of these studies were too small to adjust for confounders (Table 1) [34][35][36][37].

One major limitation of the above studies is the lack of biopsy confirmation. Instead, NAFLD was diagnosed by combinations of ultrasound, computed tomography (CT) imaging and various fibrosis/fatty liver scores. Accordingly, it is unknown how the severity of NAFLD, e.g., steatohepatitis or hepatic fibrosis, impacts cognitive function; based on the studies' inclusion criteria, patients with more advanced liver disease most likely comprised only a smaller fraction of the NAFLD groups. Another overall limitation is the use of crude neuropsychological screening tools as the majority of tests used are developed for the diagnosis of dementia and may not be sensitive towards the cognitive phenotype of NAFLD.

In conclusion, the studies discussed above do not provide sufficient evidence that the whole spectrum of NAFLD disease is independently associated with cognitive dysfunction. However, cognitive performance seems correlated with liver disease severity in NAFLD [34][36], but only a few smaller studies have investigated the impact of NAFLD severity and inflammation on cognitive function. Felipo et al. showed that patients with simple steatosis were not

cognitively impaired, whereas NASH patients (non-cirrhotic) with hyperammonemia and systemic inflammation performed poorly on all subtests of the portosystemic encephalopathy (PSE) test [38]. This indicates that simple steatosis as such may not be an independent risk factor for cognitive dysfunction and that factors associated with more severe degrees of disease, such as high ammonia levels and systemic inflammation, may be required for cognition to be affected [38].

Table 1. Evidence for cognitive dysfunction in non-alcoholic fatty liver disease.

	Design and Study Population	Controlling for Important Confounders	Diagnosis of NAFLD and Fibrosis	Neuropsychological Tests	Cognitive Domains Assessed	Main Findings	Conclusion	Important Limitations
Felipo 2012 (Spain) [38]	Cross-sectional. 40 NAFLD (*n* = 29 steatosis/*n* = 11 NASH), 54 controls.	None.	Liver biopsy.	Digit Symbol Substitution Test (DST).	Visuospatial function and psychomotor speed.	5/11 Patients with pre-cirrhotic NASH were classified as having minimal hepatic encephalopathy (MHE) on the PSE-test[1] and performed poorly on the NCT-A and NCT-B, LTT (all $p < 0.001$), and SDT ($p < 0.01$), compared with healthy controls. NASH subgroup with MHE had higher levels of	Suggests MHE-related cognitive deficits in pre-cirrhotic NASH, but not simple steatosis.	Small sample size with subgroup analysis. All NAFLD patients undergoing surgery for morbid obesity (no diabetes status). Raw data on cognitive tests missing.
				Trailmaking A test (NCT-A).	Attention and psychomotor speed.			
				Trailmaking B test (NCT-B).	Executive function.			
				Serial Dotting Test (SDT).	Attention and working memory.			

				Line Tracing Test (LTT).	Visuospatial function.	ammonia and IL-6 compared to other NASH, NAFLD, and controls.	
Seo 2016 (USA) [30]	Cross-sectional, population-based. 874 NAFLD, 3598 controls.	Age, education, diabetes, BMI, cardiovascular disease.	Ultrasound. NAFL fibrosis score (NFS*).	Simple Reaction Time Test (SRTT).	Psychomotor speed.	NAFLD patients had poor performance on the SDLT (β, 95% CI: 0.105 to 1.347) and also worse performance on the SRTT and SDST, but non-significantly so after adjusting for life-style related confounders (β, 95% CI: −0.496 to 14.679; −0.009 to 0.211).	Suggests problems with memory and attention in NAFLD.	No biopsy-proven NAFLD. Persons aged > 59 years not included.
				Digit Symbol Substitution Test (SDST).	Visuospatial function and psychomotor speed.			
				Serial Digit Learning Test (SDLT).	Memory and attention.	Poor performance on the SDST and SDLT scores were associated with increasing blood transaminases.		

Takahashi 2017 (Japan) [39]	Cross-sectional. 24 female NAFLD, 15 age-matched controls.	None.	Ultrasound.	Verbal Fluency Task (VFT).	Executive function, verbal fluency.	NAFLD patients performed significantly worse on the VFT than controls, listing on average 2 words fewer during the test (p = 0.03).	Suggests problems with executive function and semantic fluency in NAFLD.	Small sample size, no adjustment for confounding. No biopsy-proven NAFLD. Limited cognitive assessment.
Tuttolomondo 2018 (Italy) [34]	Cross-sectional. 83 NAFLD (7,5% cirrhosis, 52% NASH), 80 controls.	Age, diabetes, BMI, cardiovascular disease.	Liver biopsy (in 65%). Ultrasound, liver stiffness (transient elastography).	Mini Mental State Examination (MMSE)[2].	Visuospatial function, executive function, memory, attention, language, and orientation.	NAFLD group performed worse on the MMSE than controls, independent of confounders (mean ± SD, 26.9 ± 1.6 vs. 28.0 ± 1.4; p < 0.0001). In NASH patients, poor performance on the MMSE[2] was associated with ballooning	Suggests global reduction of cognitive function in NAFLD.	Small sample size. Limited cognitive assessment.

						(β, 95% CI: −2.65 to −0.037; p = 0.044). No difference between NASH vs. non-NASH or low fibrosis vs. high fibrosis.		
Filipovic 2018 (Serbia) [35]	Cross-sectional. 40 NAFLD, 30 controls with functional dyspepsia or irritable bowel syndrome.	Age, diabetes equally distributed between groups, but not otherwise controlled for.	Ultrasound (+ elevated ALT or AST).	Montreal Cognitive Assessment (MoCA)^3.	Visuospatial function, executive function, memory, attention, language, and orientation.	MoCA score was lower in NAFLD patients (mean ± SD, 24.07 ± 3.18 vs. 27.17 ± 2.35; p < 0.001), and NAFLD patients had a 4-fold increased risk of having an abnormal MoCA^3 score, compared with controls (RR, 95% CI: 1.815 to 8.381; p = 0.0005).	Suggests global reduction of cognitive function in NAFLD.	Small sample size, no adjustment for confounding. No biopsy-proven NAFLD.
Celikbilek 2018 (Turkey) [36]	Cross-sectional. 70 NAFLD,	Age, education, diabetes, metabolic syndrome.	Ultrasound, FIB-4 score**.	Montreal Cognitive Assessment (MoCA)^3.	Visuospatial function, executive function, memory, attention, language,	NAFLD was associated with lower MoCA score on univariate regression analysis (OR =	Suggests global reduction of cognitive function in NAFLD (mostly	No biopsy-proven NAFLD.

	73 controls.				and orientation.	2.99; p = 0.002), but not after adjusting for confounders (multivariate). MoCA score was negatively correlated with FIB-4** score.	executive and visuospatial function).	Patients with morbid obesity not included.
Weinstein 2018 (USA) [37]	Cross-sectional, population-based. 413 NAFLD (174 +T2DM), 689 controls (142 +T2DM). Age > 60 years.	Age, education, obesity, cardiovascular disease. Diabetes controlled for in subgroup analysis.	Presence of fatty liver index score*** ≥ 60.	Consortium to Establish a Registry for Alzheimer Disease – Word Learning subset (CERAD-WL).	Verbal memory (immediate and delayed recall).	NAFLD patients without T2DM did not demonstrate cognitive dysfunction, but NAFLD + T2DM performed worse than T2DM only and healthy controls on the DSST (mean ± SE, 47.1 ± 1.7 vs. 56.0 ± 1.1 and 53.6 ± 1.2). NAFLD + T2DM was associated with poor performance on DSST after	Suggests no specific cognitive impairments in NAFLD.	No biopsy-proven NAFLD. Not generalizable to younger individuals.
				Animal Fluency Test (AFT).	Executive function, verbal fluency.			
				Digit Symbol Substitution Test (DSST).	Visuospatial function,			

					psychomotor speed.	adjusting for confounders (β, 95% CI: -6.75 to -0.12; p < 0.01).		
An 2019 (USA) [37]	Cross-sectional. 23 NAFLD, 21 sex-matched controls.	None. 8/23 NAFLD patients with diabetes.	Liver biopsy (2/23 by transient elastography).	The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[4].	Immediate and delayed memory, attention, language, and visuospatial memory.	Mean RBANS total score for NAFLD patients was below mean, but within the normative range after adjusting for age and educational level.	Suggests no specific cognitive impairments in NAFLD.	No control group for cognitive assessment. Small sample size, no adjustment for confounding.
Weinstein 2019 (USA) [33]	Cross-sectional, population-based. 378 NAFLD, 1278 total.	Age, education, diabetes, BMI, cardiovascular disease.	Multi-detector CT and NAFLD fibrosis score (NFS*).	WAIS-R[5] subtest: Logical memory delayed (LMd).	Verbal memory (delayed recall).	No significant association between NAFLD and cognitive performance on any tests after adjusting for confounders, but advanced fibrosis (NFS*) was associated with poor performance on TrA – TrB (β, mean ± SE, −0.11 ± 0.05; p = 0.028) and SIM (β, mean ±	Suggests problems with executive function in NAFLD with fibrosis.	No biopsy-proven NAFLD.
				WAIS-R[5] subtest: Visual reproduction (VRd).	Visual memory (delayed recall).			
				WAIS-R[5] subtest: The Similarities test (SIM).	Abstract reasoning.			
				Trailmaking A – B test (TrA-TrB).	Executive function.			

			SE, −2.22 ± 0.83; p = 0.009).
	The Hooper Visual Organization Test (HVOT).	Visual perception.	

[1] Portosystemic Systemic Encephalopathy (PSE) test: Test battery used to diagnose minimal hepatic encephalopathy (MHE), consisting of 5 tests. Measures Portosystemic Hepatic Encephalopathy Score (PHES), sum of individual test scores measured as standard deviations outside of normal range, controlled for age. PHES < −4 = MHE. [2] Mini Mental State Examination (MMSE): Brief cognitive screening tool for dementia and mild cognitive impairment. Score 0–30, higher score indicates better performance. MMSE score < 25 = dementia. [3] Montreal Cognitive Assessment (MoCA): Brief cognitive screening tool for dementia and mild cognitive impairment. Score 0−30, higher score indicates better performance. MoCA score < 26 = dementia. [4] Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Neurocognitive battery for detection and characterization of dementia and mild cognitive impairment. Consists of 12 subtests, yielding 5 Index scores and a total score (mean ± SD, 10 ± 3; 100 ± 15). [5] Wechsler Adult Intelligence Scale - Revised (WAIS-R): Intelligence quotient test designed to measure *intelligence* and cognitive ability in *adults* and older adolescents**.**

* NFS = −1.675 + 0.037 × age (years) + 0.094 BMI (kg/m^2) + 1.13 × impaired fasting glucose (IFG) or diabetes (yes = 1, no = 0) + 0.99 AST/ALT ratio − 0.013 × platelets (×10^9/L] − 0.66 × albumin (g/dL) [40]. Probability for advanced fibrosis: NFS > 0.676 (low); 0.676 < NFS < −1.455 (intermediate) < −1.455; NFS < – 1.455 (high). ** FIB-4 score = (age (years) × AST (U/L))/(platelets (10^9/L) × √ALT (U/L)). *** Fatty Liver Index Score = $e^y/(1 + e^y)$ × 100, where y = 0.953 × ln(triglycerides (mg/dL)) + 0.139 × BMI (kg/m^2) + 0.718 × ln (GGT (U/L)) + 0.053 × waist circumference (cm) – 15.745 [41].

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