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Letter to the Editor

Paradigm of Functional Hepatology Disorders

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"*Verba docent, exempla trahunt*"
In Memory of Dr Chris Dobson, MBBS, MRCP
(1976–2024)

Dear Editor,

Functional gastrointestinal disorders (FGDs) are commonly seen in the spectrum of gastrointestinal conditions as a substrate *per se*. On the other hand, managing hepatology diseases does not typically involve targeting functional manifestations as a specific treatment goal since these are not generally considered purely functional *sui generis* disorders. Instead, they are seen as intrinsic parts of liver disease. A prominent example of this is pruritus, which may be associated with different etiologies such as primary sclerosing cholangitis, primary biliary cholangitis, or jaundice of various origins.[1] Our group of authors recognizes the necessity of clarifying this issue in depth and suggests introducing the term functional hepatology disorder (FHD) for a spectrum of diseases analogous to FGDs.

We should bear in mind that some symptoms of liver disease may not be termed functional disorders. Jaundice, for instance, might be one of the most apparent examples. One may consider jaundice as just a symptom of different diseases and therefore portray it as a functional manifestation. However, this is not entirely accurate and may lead to misunderstanding.[2] We feel jaundice is closer to a syndrome than a symptom. It encompasses a pattern of similar alterations in the body's bio-pathophysiology, which affect tissue structure (*i.e.*, morphology) and can be precipitated and replicated by various triggers. Therefore, we tend to think of jaundice as more of a syndrome than a mere symptom (*i.e.*, functional disturbance solely).

Our primer on FHD suggests that the consequences of liver diseases, which cannot be elucidated as independent entities because they lack specific bio-pathophysiological patterns of tissue morphology alteration, should be termed FHD. This term encompasses symptoms and attempts to delineate them from the disease itself. However, we recognize that symptoms are part of the disease continuum, in which morphology and pathophysiology are coherently intertwined.[3] Moreover, we propose FHD due to the increasing incidences and prevalences of all types of liver diseases, necessitating proper differentiation principles to address this burden more adequately. The symptoms we believe might be incorporated into FHD include various combinations of fatigue, low-grade fever, sphincter control disturbances, pain (both neuropathic and visceral), sensory and visual defects not explained by gross neurological degeneration or hepatic encephalopathy, weight loss not stemming from catabolism but primary anorexia, gut dysmotility (including gastro and entero-paresis with or without syndrome of intestinal bacterial overgrowth-induced dysbiosis), skin changes, blood pressure and heart rate variability not attributed to cardiomyopathy, soft tissue friability, and insomnia.[4,5] Of course, as previously stated, pruritus should also be mentioned as having qualities of a functional hepatology disorder.

In addition, muscle fibers and tissues are very sensitive to metabolic pathways influenced by disrupted liver ammonia metabolism, cirrhotic sarcopenia and osteopenia, weight loss, and anorexia. These symptoms may be considered functional since they indicate persistent liver dysfunction or liver failure.

One pathological mechanism might be serum electrolyte disturbances, which occur in the milieu of altered neurovegetative functions in the liver disease setting.[6] These electrolyte abnormalities in hepatology conditions make patients more prone to functional impairments in other organ systems. Furthermore, there is a specific inflammatory fingerprint in patients with liver diseases, especially chronic liver disease, which may underlie the pathophysiology of FHD.[3] Electrolyte differences in cirrhosis are particularly inclined to alter cell transmembrane potentials, leading to neurosensory and neuromotor alterations.[7] Most of these consequences are in a con-

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stant progressive state due to the evolving process of liver fibrosis. Different clinical manifestations and significances are thought to arise due to the inflammatory context, which results from diffuse hepatocyte injury.[3] The more extensive the injury, the more inflammatory pathways are recruited, facilitating electrolyte shifts that cause multiple functional disorders. Essentially, constantly shifting intracellular and extracellular ions in the presence of a progressive liver-specific inflammatory state are hallmarks of the FHD paradigm. Additionally, contributing factors stemming from portal hypertension and endothelial dysfunction play a role. These factors involve not only hemodynamic perturbations but also microcirculation defects with end-organ end-vascular insufficiency, leading to deleterious mechanisms via anoxic and hypoxic metabolism.[8] Consequently, all these factors result in the loss or impaired function of many other organs beyond the liver itself.

We wish to convey this theory in a reasonable and straightforward manner for readers to understand the processes underlying FHD and perhaps open a new chapter for better recognition of functional symptoms in liver diseases. We acknowledge that the liver has specificities that are beyond direct diagnostic observation compared to the gastrointestinal tract. However, this should not be a hindrance but rather a stimulus for further investigations. For instance, contrast-enhanced ultrasound scans and transient elastography could broaden the scope of liver examinations. Furthermore, high-yield non-invasive biochemical scores may prove very helpful in this setting.

In terms of treatment, there are no apparent strategies—addressing the underlying liver disease etiology should be the primary focus.[9] Pre-emptive measures for transcellular ion homeostasis should be implemented early, with interventions including crystalloid infusions, hypertonic solutions, and rational use of diuretics and aquaretics. One often overlooked treatment is diet—adequate nutrition regimens can help maintain electrolyte homeostasis in the long run.

Additionally, objectively grading the inflammatory cirrhosis-induced state might be beneficial, as overt clinical findings are often subtle and misleading.[10] Proper use of high-sensitivity C-reactive protein and early white blood cell differential counts might be useful, particularly in the first period of the disease evolution. The neutrophil-to-lymphocyte ratio provides insight into the propensity for intense inflammation or a more indolent disease pattern. These simple tests may assist in clinical pharmacologic guidance.

Our point of view stems from the analogy with FGDs. We aimed to raise awareness of the functional properties of liver disease, which cannot be solely attributed to symptoms and symptomatic findings. We advocate for a more subtle and intricate evaluation of functional hepatology disorders as a primer encompassing different functional manifestations without overt morphological alterations or apparent pathophysiology, except those already existing in liver disease. It will be interesting to read the results of ongoing investigations on this and similar topics and their conclusions. Nevertheless, many interventions could already be implemented if we first acknowledge the existence of this subset of disease functionality disturbances, making it a target in our treatment strategies. Joint effort in this endeavor is pivotal, and we suggest that more practicing clinicians ascertain the relevance of FHD in their everyday work while simultaneously conducting more research and evaluation of this novel FHD concept.

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Conflict of interest

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Author contributions

Writing, responsible for the integrity of the work as a whole (IR), original draft (VM), critical revision of the manuscript and supervision (JMN and ECR), conceptualization (NP), resources (CB), visualization (JT and SS), validation (SM and KS), investigation and literature review (IR).

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