

What Has the Optimistic Bias Got to Do with the Need to Differentiate Fatty Liver from Nonalcoholic Steatohepatitis?

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Both neuroscience and social science suggest that human beings are more optimistic than realistic [1]. On average, we expect things to turn out better than in the end they are. People hugely underestimate their chances of being diagnosed with serious illnesses and overestimate their likely lifespan. The belief that the future will be much better than the past and present is known as the optimism bias. It abides in every race, region and socioeconomic bracket. Everyone might expect optimism to erode under all the threats and failures that shape human life, but optimism about the personal future remains incredibly resilient. This attitude towards the future is based on particularly fascinating findings. In fact, there are regions in the central nervous system (CNS) - the amygdala and the anterior cingulate - becoming increasingly accurate when predicting future events. They see the world as it is. In other words, in the absence of a neural mechanism that generates unrealistic optimism, it is possible all humans would be mildly depressed. For example, after choosing between similarly valued alternatives, people rate the selected option as better than they originally did, and the rejected option as worse [2].

Nonalcoholic fatty liver diseases (NAFLD) range from the simple fatty liver (FL), generally thought to be benign, to nonalcoholic steatohepatitis (NASH), widely accepted as a progressive disease towards cryptogenic cirrhosis and hepatocarcinoma (HCC). Since the very beginning, the natural history of the disease has been poorly understood [3, 4] and the therapeutic attempts have been of little interest [5]. However, considerable progress has been made in the understanding of NASH. Thus, NASH is considered as a consequence of insulin resistance and other underlining

factors with histological findings ranging from fatty change alone to fat plus inflammation, to fat plus ballooning degeneration, and to fat plus alcoholic hepatitis-like lesions including Mallory body and fibrosis. But, what about FL? Should we bury it as a benign disease without any surprise down the line for the patients who after an imaging feature undergo liver biopsy? Is it necessary to distinguish NASH from non-NASH or FL in the spectrum of NAFLD? In other words, should physicians care for and cure non-NASH patients? Finally, the fact that we do not have any resolute cure for NASH should it prevent us from treating FL, principally considering it, as well as NASH, as a further manifestation of the metabolic syndrome (MS) [6]?

In my opinion, we are perpetrating the same mistake that was committed some decades ago when hepatologists thought of distinguishing benign chronic persistent hepatitis (CPH) from severe chronic active hepatitis (CAH). This classification of chronic viral hepatitis was constructed without knowledge of well-defined aetiological factors. Better understanding of the different hepatitis viruses has shed new light on this subject. In fact, the validity of the conventional classification has been evaluated by a comparative study of chronic viral hepatitis B and C. Authors concluded that the artificial subdivision of chronic hepatitis into CPH and CAH was obsolete and that the histological assessment of chronic hepatitis should consist of a grading of inflammatory activity (minimal, mild, moderate, severe) and staging of fibrosis (extent of distortion of architecture) [7]. The old histology-based classification is no longer considered appropriate. The concepts of grading and staging, borrowed from tumour pathology, have been widely accepted [8]. That classification of liver histology (minimal, CPH, CAH and cirrhosis) was compared with a new classification recently described by Sheuer et al in percutaneous liver biopsies from patients with chronic hepatitis C viral infections. The previously adopted classification is more often misleading even though it correlates well with the new classification and thereby permits comparisons between historically clinical studies [9].

But the concept that the CPH is benign and the CAH is progressive, without focusing the attention on the fact that they

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could be two steps of the same illness, as it is evident now, is completely changed. Coming back to NAFLD, it is very clear that I am in favour of this unified hypothesis, so why perform biopsy or use non-invasive markers? In case of non-NASH, should physicians not advise patients to be on a hypocaloric diet or to exercise or take metformin? Or should physicians ask patients for another appointment after six months hoping that the dysmetabolism could change or ameliorate? Metabolic syndrome, of which NAFLD is the mirror, is a pandemic and should be tackled by simple, rapid and reliable means having in mind the main complications that are firstly cardiovascular disease (CVD) and secondly liver cirrhosis and HCC. Hepatologists could be the first ones to evidence that MS is on the verge of appearing in their patients who suffer from non-NASH or simple FL long before they become obese or diabetics, but sufficiently early to try to do something. Therefore, the MS could be a useful additional contributor in the estimation of global cardiovascular risk beyond age, high LDL-cholesterol or other standard risk factors. The components of MS have partially overlapped mechanisms of pathogenic actions mediated through common metabolic pathways. Therefore their total combined effect could be less than the sum of the individual effects. The concept that MS is a consequence of obesity and insulin resistance provides a useful “life-style changes” approach for prevention and treatment: caloric restriction, weight-loss and increased physical activity. The next step could theoretically be pharmacological interventions such as metformin, acarbose, fibrates, weight-loss drugs (currently only orlistat is practically available) and perhaps glucagon-like peptide-1 agonists. A third step should probably be kept for bariatric surgery. Obesity is a leading risk factor for MS whose further expression is NAFLD. Metabolic syndrome is associated with a proinflammatory state that contributes to insulin resistance. Finally, a “metabolically benign obesity” that is not accompanied by insulin resistance has recently been postulated to exist. Increases in spleen size and CRP levels represent a reliable tool in diagnosing insulin resistance [10].

And, here we are with the paper by Fierbinteanu et al [11]. I believe that it is an outstanding research study according to the recent paradigm followed by the majority of hepatologists. However, I do not share the feeling of the necessity to distinguish NASH from non-NASH in order to establish a degree of severity of NASH, by histology or by surrogate markers, because it signifies the reduction of everything down to the liver and, unfortunately, it is not the case. If NAFLD were a disease confined to the liver [12], histology could be mandatory giving priority to a cost/benefit analysis to assess whether the proposed policy of using this invasive tool in differentiating the more severe form from the non-progressive one was worth doing. Anyway, liver biopsy should be considered the best available standard not the gold one due to the following evidence: it represents less than 1/50,000 of the whole organ [13]; there is an intra-observer variability as high as 25% [14] so that a right diagnosis can be lost, and a moderate inter-observer variability [15]; it is a snapshot of a fixed in time situation;

it mirrors a phenomenon (fibrosis) that is hardly static [16]; there is a large variability between the left and right lobes [17]. In fact, agreement for steatosis was excellent but only moderate for fibrosis, while concordance was only fair for most features of necroinflammation. Also, the intraobserver agreement for lobular inflammation [18] was moderate; it is not advisable in follow-ups in which various non-invasive markers, including blood tests (also a neoplastic one) [19], imaging, and novel technologies are used; it is ill-accepted by patients in every-day practice, so it does not have a great clinical significance regarding viral infection (even though being accepted by only 41% of the HCV patients) [20]; it is technically difficult to obtain from highly obese patients who are the majority of our patients suffering from NAFLD, being performed only in 4.5% of the cases [21] and this increases the risk of complications [22].

New evidence, brought by electron microscopic findings of FL and NASH, showed that ultrastructural characteristics are similar, which suggests that simple hepatic steatosis or FL may also have the potential to progress to fibrosis and cirrhosis like NASH [23]. Moreover, another group found that patients with simple hepatic steatosis or FL may still develop NASH and fibrosis progression, testified by paired repeated liver biopsies at three years [24]. It is stated that starvation strongly affects the metabolism of lipids, but it is not clear if these processes are subsequently accompanied by fibrosis of the liver tissue and how long it takes to develop. Results show that prolonged restriction is associated with the development of fibrosis of the liver tissue and could support the hypothesis that simple hepatic steatosis or FL can develop into fibrosis, first step towards NASH/cirrhosis [25]. In another study, obese C57BL/6 mice were fed with high fat and cholesterol diet (HFC) for 6, 16 and 26 weeks. The evidences of gene expression profile, elevated serum alanine aminotransferase, and histological data support a progression from the simple FL to the more severe NASH in these HFC-fed mice within the time frame of 26 weeks, demonstrating that the severity of NAFLD is a time-dependent variable [26]. Ratziu et al reported on a series of six patients with a biopsy-proven isolated steatosis followed-up by performing a second biopsy five years after. All but one of the initial biopsy samples were adequate, i.e., longer than 1.5 cm. At follow-up, inflammation and ballooning were detected in all patients and mild fibrosis in three out of five. Mostly interesting, progression to NASH occurred independent of ALT activity elevation. Five patients showed further metabolic risks during the follow-up: increase in body mass index, triglyceride levels, HOMA or presence of arterial hypertension. Only one patient did not exhibit progression, even though he was still exposed to metabolic risks factors at the end of the follow-up. This report demonstrated that isolated steatosis was not necessarily a benign, non-progressive condition [27]. A further confirmation comes from a recent study on 50 NAFLD patients, well characterized by histology which showed that the hepatic venous pressure gradient was normal in 27 patients (54%), borderline (5 mmHg) in 9 (18%) and

elevated in 14 patients (28%). Nine of these latter patients had fibrosis score 0. The degree of steatosis and not of fibrosis was the only independent predictor of the presence of portal hypertension [28].

I would hope that hepatologists will never have the opportunity to say: we simply should have evaluated this fatty liver pessimistically.

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