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The Pathology of Liver Disease Caused by Substances Other than Alcohol

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ABSTRACT:-

In the absence of alcohol consumption, non-alcoholic fatty liver disease (NAFLD) refers to a range of lesions from steatosis (non-alcoholic fatty liver, or NAFL) to a complicated pattern including hepatocellular injury and inflammation (non-alcoholic steatohepatitis, or NASH). It is becoming more evident, though, that there might be some intermediary patterns. Since a specific definition of each group is crucial, the histological assessment of liver biopsy samples is essential in the diagnosis of NAFLD and NASH in the absence of adequate non-invasive procedures. In a suitable clinical setting, patients can be classified as having NAFLD if at least 5% of their hepatocytes show steatosis. The lesion is typically classified as NASH when lobular inflammation and liver cell clarification/ballooning are also present. Since fibrosis stage is the primary predictor of prognosis for this condition, evaluating it is even more important than necroinflammation. Although semi-quantitative histological grading methods for NAFLD have been proposed, they are not practical in clinical practise and each has certain drawbacks. For thoroughness, we advise using the SAF (Steatosis, Activity, Fibrosis) score, which evaluates each of the three histopathological lesions in NAFLD separately based on the degree of steatosis (S, from S0 to S3), degree of activity (A, from A0 to A4 by adding grades of ballooning and lobular inflammation, both from 0 to 2), and stage of fibrosis (F from F0 to F4).

Keywords: non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, fibrosis, liver biopsy.

INTRODUCTION: -

Globally, the prevalence of non-alcoholic fatty liver disease (NAFLD) is rising quickly at the same time as obesity [1]. Non-alcoholic fatty liver, also known as NAFL, is a general term for a spectrum of lesions that range from pure steatosis without significant necroinflammatory injury to a complex pattern of lesions that include active lesions of hepatocyte injury, apoptosis, cell death, and inflammation (also known as non-alcoholic steatohepatitis, or NASH) when alcohol is not consumed. Steatosis and steatohepatitis can be seen in non-alcoholic patients in a number of clinical settings, with obesity, type II diabetes, and lipodystrophy being the most common causes of liver disorders linked to insulin resistance. Infection with the HCV, drug use, malnutrition, Wilson disease, and other uncommon disorders may also be linked to them. However, due to its great frequency, liver

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disease linked to the metabolic syndrome or one of its components is typically referred to by the acronyms NAFLD and NASH by hepatologists [2].

DISCUSSION:-

LIVER BIOPSY IN NAFLD: LIMITATION AND INDICATIONS

A key benefit of obtaining a liver biopsy in a patient with clinical indications of NAFLD is to confirm (or exclude) the diagnosis of NASH. Histopathological assessment of liver biopsy samples remains important to all investigations in NAFLD [3]. When compared to non-invasive tests, liver biopsy plays a special function since it allows for a difference between processes that are thought to be non- or slowly progressing (steatosis alone, NAFL) and characteristics linked to the development of liver injury (steatohepatitis, NASH). The risk of morbidity and mortality from liver biopsy is low yet real, and it is an intrusive surgery. Thus, liver biopsy cannot be regarded as a screening procedure and should instead be restricted to chosen patients, especially for clinical trials, due to the enormous number of people with suspected NAFLD [4, 5]. In addition to the possibility of unfavourable outcomes, liver biopsy has inherent limitations that could lead to failure. The liver is not always afflicted evenly, as has been shown in numerous different chronic liver disorders, and sampling variation is a pertinent concern given that the size of a needle biopsy sample only reflects a small portion of the overall organ. In fact, a liver biopsy's appropriateness is determined by the size of the core; if the sample is too tiny, a significant misdiagnosis and staging mistake may ensue [6].

While a 15 mm long biopsy delivers very reliable information, a 25 mm length sample is thought to be ideal for providing a complete quantitative assessment of a lesion. The diameter of the core must also be taken into account in addition to the length. In fact, the lobule is frequently transected by narrow-bore needles, making it impossible for the pathologist to analyse all of its components and challenging to determine architectural distortion. A 16-gauge needle (or bigger) is regarded as sufficient. Another crucial factor is the pathologist's experience who does the evaluation. General pathologists can do just as well if they receive the right training, even though liver pathologists with greater experience provide more reproducible findings [7].

Large-scale studies have demonstrated that patients with steatosis alone do not have an elevated risk of liver disease mortality compared to the general population, however those with NASH or severe fibrosis do [8]. There could be many liver diseases present, which is another clinical situation. There is histological evidence of concomitant steatohepatitis in up to 5% of individuals with another liver illness, such as chronic hepatitis C, autoimmune liver disease, or primary biliary cirrhosis, according to large biopsy series [9].

Similar to this, steatohepatitis and cirrhosis have been reported in up to 25% and 1-3% of morbidly obese individuals after bariatric surgery, respectively, and are frequently discovered incidentally, making biopsy an indication in these circumstances [10, 11]. The provision of a semi-quantitative assessment of the severity of damage is the liver biopsy's ultimate objective

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(see below). Although these grading methods are now of limited value in everyday practise, they are quite helpful in clinical trials [4, 12, 13].

THE PATHOLOGY OF NAFLD:-

Non-alcoholic fatty liver (NAFL): Steatosis alone or steatosis with modest accompanying lesions that are not severe enough to be categorised as NASH define people with non-alcoholic fatty liver. According to epidemiological research, persons with steatosis alone are less likely to die from liver-related causes of disease but are more likely to experience the effects of cardiovascular or nonhepatic cancer-related illnesses [14]. Patients who have steatosis but minor accompanying abnormalities, such as a few inflammatory cells or normal-sized clarified/ballooned hepatocytes, are a subgroup of patients. Although it is widely acknowledged that this lesion is NAFL, it is not known whether the prognosis is as benign as pure steatosis. While some prospective investigations have showed that these lesions may stabilise or even regress, retrospective studies have revealed that certain cases can progress to more severe illness, albeit at a slower rate than those with NASH [15].

Non-alcoholic steatohepatitis (NASH): It is obvious that patients who have a histological pattern of steatohepatitis and advanced fibrosis have a substantially higher risk of developing end-stage liver disease or liver-related death, even though the natural history of NAFLD and NASH is still poorly understood [16, 17, 18]. Uncertainty exists regarding the connection between steatosis and steatohepatitis. Epidemiological data indicate that there are two distinct entities with a probable shift from one to the other and in both directions, notwithstanding the possibility of progression from pure steatosis to steatohepatitis. As previously mentioned, steatohepatitis is a pattern of liver damage that necessitates a liver tissue examination. There are no non-invasive tests that can reliably identify patients with steatohepatitis or distinguish steatohepatitis from pure steatosis, despite the fact that numerous algorithms based on a mix of clinical and biological data have been presented [19]. Therefore, if a liver biopsy is required to determine whether NASH is present, it must be done.

Lobular inflammation: Small clusters of inflammatory cells, primarily lymphocytes and macrophages, cause lobular inflammation. These cells are occasionally accompanied by hepatocyte dropout or apoptotic bodies. Neutrophil aggregations are uncommon and only stand out when numerous Mallory-Denk bodies are present. Ordinarily, lobular inflammation is minor; however, when it is severe, additional or related reasons, such as alcohol or drug toxicity, may be present. According to the amount of inflammatory foci in a certain area, the NASH Clinical Research Network (NASH CRN) has defined a 4-tier grading system (from grade 0 to 3); however, the SAF (Steatosis, Activity, Fibrosis) scoring system has recommended a 3-tier grading system (from grade 0 to 2) instead [20].

Ballooning hepatocellular injury: The other primary hallmark of steatohepatitis for diagnosis is ballooning hepatocellular damage. The elimination of sharp angles in the liver cell results in balloon-shaped hepatocytes, which have a transparent, flocculent, non-vacuolar

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cytoplasm. Hepatocytes could be bigger than typical hepatocytes or they might not be. While the SAF score bases its inflated cell evaluation mostly on the size of the cells, the NASH CRN system bases its ballooned cell evaluation primarily on number (none, few, many).

Fibrosis: Fibrosis is a significant characteristic since the majority of research have demonstrated that, regardless of the presence or severity of other histological findings, the stage of fibrosis predicts overall- and liver-related mortality independently [20]. Even though fibrosis of any level can be present in NAFL without any signs of NASH, NASH is often always accompanied with some degree of it. Fibrosis in these patients is now thought to be a type of NASH that is in remission.

NASH and grading of activity: Possibly the most contentious issue is this one. The NIDDK NASH CRN suggested the NAFLD Activity Score (NAS), which is based on the idea that in liver disease, necroinflammatory lesions and the degree of fibrosis should be evaluated independently since the former may be more reversible than the latter. Steatosis, lobular inflammation, and ballooning were the lesions that were most closely associated with the diagnosis of NASH based on the examination of many sets of biopsies. As a result, the NAS was developed as an unweighted score for ballooning, lobular inflammation, and steatosis (0–3). (0-2). It has been used repeatedly as a criterion for identifying NASH and for the inclusion or exclusion of patients in clinical studies, despite repeated warnings from NASH CRN that the numerical value should not be seen as a replacement for the pathologist's diagnosis [21]. The assumption is that NAS will reflect the course of the disease and offer a more precise definition than the basic distinction between NASH and NAFLD without NASH. It becomes sense, then, to anticipate a strong relationship between a relevant activity score and the occurrence of NASH. The NAS activity score was actually found to be supported by the fact that the majority of biopsies with a total NAS 5 were connected with the diagnosis of confirmed steatohepatitis [22] Despite this, and even though there is a large grey area (NAS 3-4) in which NASH may or may not be present, NAS raises the probability of NASH. In fact, the inclusion of steatosis in the NAS is responsible for the difference between NAS and NASH. It is unclear why harmful characteristics like liver cell destruction and lobular inflammation should be linked to steatosis, whose harmful effects have not been conclusively demonstrated.

CONCLUSION:-

In the absence of alcohol consumption, non-alcoholic fatty liver disease (NAFLD) refers to a range of lesions from steatosis (non-alcoholic fatty liver, or NAFL) to a complicated pattern including hepatocellular injury and inflammation (nonalcoholic steatohepatitis, or NASH). It is becoming more evident, though, that there might be some intermediary patterns. Since a specific definition of each group is crucial, the histological assessment of liver biopsy samples is essential in the diagnosis of NAFLD and NASH in the absence of adequate non-invasive procedures. The SAF score, which evaluates each histological lesion's degree of steatosis (S, from S0 to S3), grade of activity (A, from A0 to A4 by adding grades of

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ballooning and lobular inflammation, both from 0 to 2), and stage of fibrosis (F, from F0 to F4), is recommended for comprehensive reasons.

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