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Review Article

Autoimmunity and liver disease: Updates of the literature

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Abstract:

Progressive immune-mediated inflammation and eventual destruction of hepatocytes and biliary epithelial cells characterize autoimmune liver diseases (AILDs). The primary objective of this study was to conduct a literature review on AILDs. In a nutshell, autoimmune liver diseases are a group of disorders in which the body's immune system assaults the liver cells in error, causing inflammation and damage. Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis are the three most prevalent autoimmune liver diseases (PSC). AIH is a chronic disease characterized by inflammation and liver cell injury, which, if left untreated, can progress to cirrhosis and liver failure. PBC is a chronic disease that affects the small bile ducts within the liver and can contribute to cirrhosis, liver failure, and other complications. Chronic PSC, which affects the larger bile ducts, can cause liver failure and bile duct carcinoma. The precise cause of autoimmune liver diseases is unknown, but genetic and environmental factors are believed to play a role. Typically, blood tests, imaging, and liver biopsies are used for diagnosis. Medications that suppress the immune system, such as corticosteroids, immunosuppressants, or biologics, may be used in the treatment of a specific disease. In some instances, liver transplantation may be required. Autoimmune liver diseases can have a significant impact on a person's quality of life and require ongoing management and monitoring. It is essential for individuals with these conditions to work closely with their healthcare providers to manage symptoms, prevent complications, and preserve liver health overall.

Keywords: autoimmune liver diseases; immune system; liver cells; autoimmune hepatitis; primary biliary cholangitis

An overview of liver disease and autoimmunity

Both autoimmune illness and liver disease are conditions that are closely related to one another and can have a substantial impact on an individual's quality of life as well as their overall health [19]. The liver is an important organ that is responsible for several key tasks in the body, including the process of metabolism, detoxification, and the production of proteins [3]. These functions are hindered whenever the liver is injured or diseased, which in turn leads to a wide variety of symptoms and problems. On the other side, autoimmunity is a disorder in which the immune system erroneously assaults the body's own tissues, including the liver. This can lead to serious health complications. We shall investigate the connection between autoimmunity and liver disease, as well as their respective causes, symptoms, diagnoses, and treatments, in the following article [4]

Autoimmune liver diseases (AILDs)

The term "autoimmune liver disorders" refers to a collection of ailments in which the liver is attacked by the body's immune system, resulting in inflammation and damage to the organ. Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) are the three most common forms of autoimmune liver diseases (AILDs) [14]. AIH, also known as autoimmune hepatitis, is a chronic inflammatory disease of the liver that mostly affects women and has the potential to result in cirrhosis and liver failure. PBC is a chronic liver disease that worsens with time and primarily affects women. It is distinguished by the degeneration of the liver's tiny bile ducts. PBC is also known as polycystic liver disease. PSC is a chronic disease that worsens over time and can affect either men or women. It is distinguished by inflammation and scarring of the bile ducts both inside and outside of the liver [6]. The increasing immune-mediated inflammation and eventual death of hepatocytes and biliary epithelial cells that characterize autoimmune liver disorders (AILDs) set these conditions apart from other liver conditions [30]. Although overlap syndromes are possible, it most commonly refers to autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) [31]. IgG4-sclerosing cholangitis and IgG4-autoimmune hepatitis are examples of the immunoglobulin G (IgG4)-related hepatobiliary illnesses that make

up a minor percentage of autoimmune liver diseases (AILDs) [32]. Patients who have damage to their livers that cannot be reversed have the option of undergoing liver transplantation, often known as LT. The indications for liver transplantation in individuals with AILDs are, with a few notable differences, comparable to those in patients with other chronic liver illnesses [33]. These autoimmune hepatobiliary illnesses account for around 24 percent of all liver transplants, which places them in the third spot on the list of most transplant centers' most prevalent liver transplant indications [34]. Although the therapeutic approach for each autoimmune liver disease must be different, the goals of treatment remain the same: to increase the recipient's chance of survival, to prevent the failure of a liver graft, and to lower the likelihood that the disease would return. In order to accomplish these objectives, there are a number of factors that need to be taken into consideration, such as determining post-LT risk factors that correlate with liver graft failure and disease recurrence, choosing the immunosuppressive regimen that is the most appropriate, and implementing additional cancer surveillance depending on the LT indication [33].

Autoimmune hepatitis (AIH)

AIH is a complicated inflammatory liver disease that has an unknown cause and is caused by a mix of immunologic, genetic, and environmental variables. The exact cause of AIH is unknown. The incidence of ischemic heart disease in adults is extremely variable around the globe, ranging from 4.2 occurrences per 100,000 people in Singapore to 42.9 cases per 100,000 people in Alaska [32]. In the United States, a population-based national survey that was conducted not long ago found an estimated prevalence of 31.2 cases per 100,000 individuals [38]. The clinical presentation might take many different forms. Individuals may exhibit no symptoms, acute symptoms (such as abrupt severe or acute liver failure), or mild symptoms that may progress to chronic manifestations of the disease. The diagnosis is challenging and requires certain test signs such as increased total immunoglobulin G levels and raised aminotransferase levels; lymphoplasmacytic interface hepatitis on histology; and the presence of autoantibodies in the serum (antinuclear antibodies, anti-smooth muscle antibody, and anti-liver kidney microsomal antibodies). It is important to rule out other liver illnesses such as viral hepatitis, Wilson's disease, genetic liver injuries, and metabolic liver injuries [39]. Even if the AIH care guidelines are updated on a regular basis, a sizeable portion of patients who have AIH may eventually develop liver disease of the end-stage and will be in need of an LT. Five percent of all LT operations carried out in the United States are classified as AIH [33]. The patient survival rate is 76 percent after five years, whereas the transplant survival rate is 70.9 percent [40]. These rates are quite good; nevertheless, when compared to those of other LT indications, there is still a larger chance of late acute rejection (9%) and chronic rejection (16%), as well as recurrent sickness (36% to 68% after five years) [41]. The diagnosis of AIH that occurs repeatedly can be challenging (rAIH). It can be challenging to differentiate between rAIH and graft rejection due to a number of circumstances, including the use of immunosuppressive medicine and the relatively short duration of the condition. These two disorders can be differentiated from one another with the use of the characteristics of the biopsy [40]. Determining the immunosuppressive maintenance therapy that is most suitable for an individual with AIH after they have received LT is the most crucial part of their care. Transplant hospitals are adopting new immunosuppressive regimens in order to balance the potential influence that immunosuppressants may have on the long-term morbidity and mortality of AIH patients following LT. In individuals diagnosed with AIH, the results of post-LT treatment have been recorded in a number of systematic reviews and meta-analyses [32,42]. Despite this, management results are still limited, which makes it challenging to provide management recommendations based on information of a high quality. Autoimmune hepatitis, often known as AIH, is a form of chronic immunoinflammatory liver disease that can present itself in a number of different ways. The incidence of autoimmune hepatitis (AIH) has been rising at an alarming rate all over the world, and a corresponding increase in the number of male patients has also been seen. For the purpose of diagnosing autoimmune hepatitis (AIH), serum biochemistry and liver histology are utilized. Symptoms of AIH include elevated aminotransferases and serum immunoglobulin G (IgG), serum anti-nuclear antibody or serum anti-smooth muscle antibody, and interface lymphoplasmacytic hepatitis. Clinical symptoms might vary depending on the disease subtype and the time frame, such as acute ischemic heart disease (AIH) with a chronic slow onset and acute ischemic heart disease with an abrupt onset (the diagnosis of which is often challenging due to the lack of typical serum findings). Because there are no illness-specific biomarkers or histological evidence, the disease phenotype may be enlarged to cover drug-induced AIH-like liver injury. This is due to the fact that there are no disease-specific biomarkers. Corticosteroids and azathioprine are the medications that are used in the initial stages of treatment for AIH. The complete normalization of aminotransferases and serum IgG is an essential therapeutic response that must occur in order to ensure long-term overall survival. When these treatments only cause a partial response or intolerance, particularly in the case of mycophenolate mofetil, the next suggested treatment is a second-line therapy. The vast majority of patients will need to continue taking maintenance medication for the rest of their lives; however, those individuals who achieve extended and stringent biochemical remission with normalized alanine aminotransferase and IgG levels may be able to discontinue using the medication. In the future, personalized medicine should be utilized to manage the quality of life of AIH patients. This should include the correct selection and dose of first-line therapy, maybe alternating with prospective medicines, aswell as the prediction of treatment withdrawal success [43]. As shown in figure (1), a schematic model of the progression and transition of AIH is presented. A representation in schematic form depicting the development and evolution of AIH. It is possible for acute-onset and acute exacerbation of autoimmune hepatitis to resolve into chronic autoimmune hepatitis, if not all cases. Drug-induced liver injury (DILI), drug-induced autoimmune hepatitis (DIAIH), non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis (AIH), acute severe (AS), and acute liver failure (ALF) are the abbreviations used to describe these conditions.

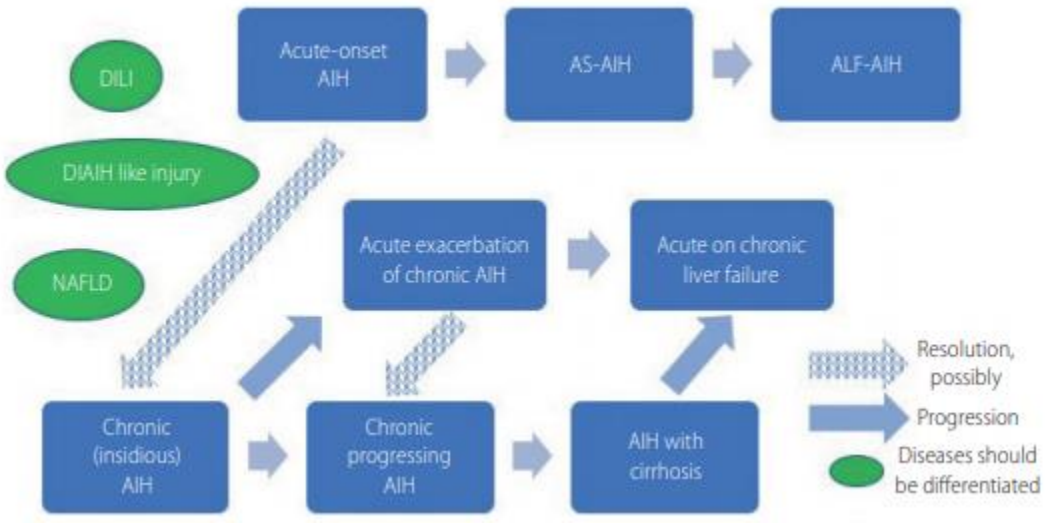

Figure: A schematic model of the progression and transition of AIH. Acute-onset and acute exacerbation of AIH may resolve to chronic AIH, if not all. DILI, drug-induced liver injury; DIAIH, drug-induced autoimmune hepatitis; NAFLD, non-alcoholic fatty liver disease; AIH, autoimmune hepatitis; AS, acute severe; ALF, acute liver failure (Alkhatib, 2022a, b).

Etiology of AILDs

Autoimmune liver diseases, often known as AILDs, are complicated ailments that arise as a consequence of a confluence of hereditary and environmental influences. Researchers have found a number of risk factors that contribute to an increased likelihood of having AILDs, despite the fact that the specific cause of AILDs is not completely understood [34]. Aspects of Heredity Researchers have found a number of genes that contribute to an increased likelihood of having AILDs. For example, the HLA class II genes have been connected to an increased chance of developing autoimmune hepatitis (AIH), which is a form of liver illness. Interleukin-12 (IL-12) is one example of a gene involved in immune modulation that has been linked to an increased risk of developing primary biliary cholangitis (PBC) [8]. Environmental Factors Environmental variables, such as being exposed to particular viruses or poisons, have the potential to provoke an immune system response that targets the liver. For instance, in autoimmune hepatitis, being exposed to particular viruses like hepatitis B or C can cause the immune system to launch an attack on the liver. When it comes to PBC, being exposed to environmental pollutants like the chemicals that can be present in cigarette smoke can potentially raise the risk of having the condition [3,9]. Diagnostic procedures for AILDs Blood tests, liver biopsies, and imaging studies are often used in conjunction with one another to arrive at a diagnosis of an AILD. Blood tests are able to determine whether or not autoantibodies are present in the body. Autoantibodies are antibodies that attack the body's own tissues. Blood tests, for instance, can show the presence of antinuclear antibodies (ANA), smooth muscle antibodies (SMA), or liver-kidney microsomal antibodies in a patient with autoimmune hepatitis (AIH) (LKMA). Blood testing could show the existence of antimitochondrial antibodies (AMA) in patients diagnosed with PBC [10]. A tiny tissue sample from the liver is taken in order to conduct an examination during a liver biopsy. A diagnosis of AILDs can be assisted with the use of a liver biopsy, which can indicate inflammation, scarring, or damage to the liver. For instance, in PBC, the typical loss of the tiny bile ducts in the liver can be seen with a liver biopsy. [Citation needed] [11]. In addition, imaging examinations such an ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) can be utilized in the diagnostic process of AILDs. Imaging examinations can disclose the size and form of the liver, in addition to revealing whether or not there is inflammation or scarring in the organ. Imaging investigations, for instance, can show, in cases of primary sclerosing cholangitis (PSC), the distinctive inflammation and scarring of the bile ducts both inside and outside the liver [11]. In a nutshell, AILDs are complicated illnesses that emerge as a consequence of a confluence of hereditary and environmental risk factors. Researchers have found a number of risk factors that contribute to the increased likelihood of having AILDs, despite the fact that the specific cause of AILDs is not completely understood. Blood tests, liver biopsies, and imaging studies are often used in conjunction with one another to arrive at a diagnosis of an AILD. A prompt diagnosis and therapy are both requirements for effective AILD management and the prevention of long-term damage to the liver.

Autoimmunity and Non-Autoimmune Liver Diseases

The development of liver illnesses that are not caused by autoimmunity, such as viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease, may also be influenced by autoimmune processes (NAFLD). When the immune system reacts to a viral infection by attacking the liver, this condition is known as viral hepatitis. Hepatitis B virus (abbreviated as HBV) and hepatitis C virus (abbreviated as HCV) are two of the most frequent viruses that cause viral hepatitis around the world [12].

In cases of viral hepatitis, the body's immune system makes an attack on infected liver cells in an effort to eradicate the virus. Nevertheless, this immune response can sometimes become dysregulated and assault healthy liver cells as well, which can result in damage to the liver as well as inflammation of the liver. If treatment is not sought, this can lead to chronic hepatitis, cirrhosis, and even cancer of the liver (Bataller and Brenner, 2015).

Another prevalent cause of liver disease all around the world is alcoholic liver disease, also known as ALD. Use of alcohol over a long period of time can cause damage and inflammation to the liver, which can eventually lead to cirrhosis and liver failure. Several studies have provided evidence to support the hypothesis that autoimmunity is involved in the pathogenesis of ALD. According to a number of studies, people diagnosed with ALD frequently exhibit high levels of autoantibodies, which is evidence of an abnormally dysregulated immune response (Gao and Bataller, 2011).

The non-alcoholic fatty liver disease (NAFLD) is a prevalent liver condition that has been linked to insulin resistance, metabolic syndrome, and obesity. Recent research has revealed that autoimmunity may be implicated in the pathogenesis of nonalcoholic fatty liver disease (NAFLD), even if the precise processes that underlie the pathogenesis of NAFLD are not completely understood. Anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and anti-liver cytosol antibodies (ALCA) are some of the autoantibodies that have been linked to non-alcoholic fatty liver disease (NAFLD). Other autoantibodies include anti-smooth muscle antibodies (ASMA) and anti-liver cytosol antibodies (ALCA) (Petta et al., 2016; Wang et al., 2018). In conclusion, autoimmunity is a factor that can play a role in the etiology of both autoimmune liver disorders and non-autoimmune liver illnesses. In the case of viral hepatitis, the immune system launches an assault on the liver in response to an infection caused by a virus. On the other hand, in the case of non-autoimmune liver illnesses such as ALD and NAFLD, autoimmunity may contribute to the development of the disease. In order to get a complete understanding of the mechanisms that underlie the role that autoimmunity plays in the etiology of liver disorders, additional research is required.

Symptoms and Diagnosis of AILDs

The signs and symptoms of autoimmune illness and liver disease might change depending on the nature of the disorder and the degree to which it has progressed. A number of symptoms, including exhaustion, abdominal pain, jaundice, and itching, are associated with autoimmune liver disorders (AILDs). Pain in the joints, rashes, and problems with thyroid function are some of the other symptoms that may be present in autoimmune hepatitis (AIH). Itching, dry eyes, and dry mouth are some of the symptoms that may be present in patients who have primary biliary cholangitis (PBC). Abdominal pain, fever, and chills are some of the possible symptoms of primary sclerosing cholangitis (PSC), which can also be abbreviated as PSC [17]. Hepatitis caused by viruses can cause a wide range of symptoms, including lethargy, fever, abdominal pain, nausea, vomiting, and yellowing of the skin and eyes (jaundice). In cases of acute viral hepatitis, symptoms often disappear after a few weeks to a few months have passed. On the other hand, those who have chronic viral hepatitis may only experience minimal or no symptoms at all, and the condition may develop slowly over the course of several years, eventually leading to liver cirrhosis and liver failure (Wang et al., 2018). Jaundice, stomach pain, nausea, vomiting, and an enlarged liver are some of the symptoms that can accompany alcoholic liver disease (also known as ALD). In severe cases of ALD, other symptoms, such as confusion and disorientation, as well as hepatic encephalopathy, may also be present [19]. Fatigue, abdominal pain, an enlarged liver, and high levels of liver enzymes on blood tests are some of the symptoms that may be present in nonalcoholic fatty liver disease (NAFLD). Jaundice, ascites, and hepatic encephalopathy are some of the additional symptoms that may be present in nonalcoholic steatohepatitis (NASH), which is a more severe type of NAFLD [20,26]. In conclusion, the symptoms of autoimmune conditions and liver diseases can vary widely and may be determined by the particular type of condition as well as the degree to which it is affected. Recognizing and treating symptoms as soon as they appear is critical for maximizing clinical outcomes and minimizing the risk of consequences. The diagnosis of AILDs is often accomplished by a multi-step process that includes a physical exam, blood testing, imaging scans, and a liver biopsy. Blood tests are utilized in order to evaluate liver function and identify the existence of autoantibodies. Autoantibodies are defined as antibodies that target the body's own tissues. Blood tests may reveal elevated liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in patients who have AILDs, in addition to the presence of autoantibodies such as antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), and anti-liver/kidney microsomal antibody type 1 (anti-LKM-1) in some cases [19]. Imaging investigations such as ultrasound or MRI may also be utilized in order to analyze the liver and discover any evidence of inflammation, scarring, or other abnormalities in the organ's function. The results of these tests can provide information on the size, shape, and texture of the liver, in addition to the presence or absence of any nodules or masses (Dyson et al., 2014). A liver biopsy could be required in some situations in order to establish a diagnosis or determine the level of liver damage that has occurred. A liver biopsy involves the removal of a tiny sample of liver tissue, which is then examined under a microscope for indications of inflammation, fibrosis, or any other abnormalities [23]. Hepatitis caused by viruses is another prevalent cause of liver disease. Blood tests are commonly used to diagnose viral hepatitis. These blood tests look for high levels of liver enzymes as well as viral antibodies, such as hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) antibody [24]. Consuming an unhealthy amount of alcohol over a long period of time can result in alcoholic liver disease (ALD), which can progress to cirrhosis, inflammation, and scarring of the liver. Imaging examinations such as ultrasound, CT scans, or MRIs have the potential to reveal an enlarged liver as well as symptoms of inflammation. These signs include increased echogenicity or lower attenuation (Mathurin et al, 2015). The disorder known as nonalcoholic fatty liver disease (NAFLD) is characterized by an accumulation of fat in the liver, which ultimately results in inflammation and liver damage. Imaging studies such as ultrasound or MRI have the potential to disclose the presence of fat in the liver, in addition to identifying symptoms of inflammation, fibrosis, or cirrhosis [26]. To summarize, a physical examination, blood tests, imaging scans, and a liver biopsy may all be necessary steps in the diagnostic process for liver illness. The specific tests that are carried out will be determined, in part, by the presumed root cause of the liver illness.

Treatment of AILDs

In certain instances, anti-inflammatory drugs like corticosteroids or pentoxifylline may be prescribed to the patient in order to reduce the level of inflammation and improve liver function. The treatment for nonalcoholic fatty liver disease may involve making adjustments to one's lifestyle, such as losing weight, modifying one's diet, and engaging in regular exercise, in order to improve insulin resistance and reduce fat in the liver. In advanced cases, it may be possible to enhance liver function with the help of drugs such as vitamin E or pioglitazone, and they can also help reduce inflammation [17].

In severe situations of liver disease or liver failure, liver transplantation may be required to save the patient's life. This is a crucial point to keep in mind. Those with autoimmune liver disease who do not respond to medical treatment have the option of undergoing liver transplantation, which has been demonstrated to be an effective therapeutic option. In cases of advanced liver disease or liver failure caused by viral hepatitis that cannot be treated with antiviral medication, a liver transplant may be required. In situations of alcoholic liver disease, liver transplantation may be explored in some circumstances; however, sobriety is required in order for this option to be considered [28,29].

Summary

Both autoimmune illness and liver disease are disorders that can affect the liver and, if left untreated, can cause persistent inflammation as well as damage to the organ. An examination of the patient's physical condition, along with blood tests, imaging scans, and possibly even a liver biopsy, are the standard diagnostic procedures. An autoimmune response can cause autoimmune liver disorders (AILDs), which include autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, among others. Immunosuppressant drugs might be used in the treatment of AILDs. Hepatitis, which is caused by viruses, alcoholic liver disease, and nonalcoholic fatty liver disease are additional potential triggers for liver disease. The treatment for these disorders varies, but some of the options include taking antiviral medicine, quitting drinking alcohol, making changes to one's way of life, and in rare instances, getting a liver

transplant. While developing an unique treatment strategy for each patient, it is frequently important to use a multidisciplinary approach and involve a group of healthcare specialists working together as a team.

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