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AUTOIMMUNE HEPATITIS: DIAGNOSTIC CHALLENGES AND RISK FACTORS – A NARRATIVE REVIEW

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ABSTRACT

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of unclear etiology, characterized by loss of immune tolerance to hepatocyte antigens in genetically predisposed individuals. Despite global occurrence and increasing prevalence, no uniform pattern of environmental triggers or genetic susceptibility has been established. Clinically, AIH demonstrates marked heterogeneity, ranging from asymptomatic biochemical abnormalities to acute liver failure or advanced cirrhosis at presentation, posing significant diagnostic challenges.

Diagnosis relies on a combination of serological, biochemical, and histopathological findings. Although autoantibodies and elevated immunoglobulin G levels remain key diagnostic markers, their limited specificity and occasional absence—particularly in acute presentations—complicate clinical assessment. Liver biopsy continues to play a central role in diagnosis, disease staging, and therapeutic decision-making, despite the growing availability of noninvasive methods. Histopathological features such as interface hepatitis, plasma cell infiltration, and lobular inflammation support the diagnosis but are not pathognomonic.

The pathogenesis of AIH involves complex immune dysregulation, including T-cell–mediated responses, impaired regulatory mechanisms, and aberrant antigen presentation. Emerging evidence highlights the potential contribution of intestinal barrier dysfunction and gut microbiota alterations to disease development and progression, although the underlying mechanisms remain incompletely understood.

Genetic predisposition, particularly within the HLA region, along with female sex and age-related factors, contribute to disease susceptibility. Additionally, AIH may coexist with other autoimmune conditions, further complicating its clinical course and diagnosis.

In summary, AIH remains a diagnostically challenging and clinically diverse disease requiring a multidisciplinary approach. Advances in immunology, histopathology, and microbiome research may improve understanding of disease mechanisms and facilitate the development of more precise diagnostic and therapeutic strategies.

KEYWORDS

Autoimmune Hepatitis, Diagnosis, Histopathology, Autoantibodies, Risk Factors, Liver Disease

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Epidemiology

AIH is a global condition and, despite some regional variability, no consistent pattern of distinct genetic susceptibility or clearly defined environmental triggers has been established. Most epidemiological studies report an annual incidence of approximately 1–2 cases per 100,000 individuals and a prevalence of around 20 per 100,000 in the general population, based on data from Europe, the Americas, and Asia, with slightly lower rates observed in Asian populations.[1-3] More recent evidence from the United States, derived from a cohort of over 18 million insured individuals, indicates a prevalence of 26.6 per 100,000 persons and an incidence of 4.0 per 100,000.[4,5]

Furthermore, the burden of AIH appears to be increasing—paralleling trends observed in other autoimmune diseases—with a growing proportion of cases identified among older individuals. [6-8]

Pathophysiological Background and Clinical Presentation

The pathogenesis of AIH involves a loss of immune tolerance toward hepatocyte antigens in genetically predisposed individuals. Autoreactive CD4+ and CD8+ T lymphocytes, along with autoantibody-producing B cells, play a central role in perpetuating liver inflammation. Regulatory T-cell dysfunction and aberrant antigen presentation contribute to sustained immune activation. Although these immunological mechanisms underpin the disease, they are not directly measurable in routine clinical practice, complicating diagnostic efforts.

Instead, clinicians rely on surrogate markers such as autoantibodies, IgG levels, and histological features, which lack absolute specificity. [2,3]

AIH exhibits remarkable clinical heterogeneity. Patients may present with: asymptomatic elevations of aminotransferases, non-specific symptoms such as fatigue, malaise, and arthralgia, acute hepatitis with jaundice, fulminant hepatic failure, decompensated cirrhosis at initial diagnosis. Acute-onset AIH may mimic viral or drug-induced hepatitis, often with normal IgG levels and absent autoantibodies, further complicating early diagnosis.[4-6]

Serological Markers and Diagnostic Challenges

Autoantibodies

The clinical history of patients diagnosed with AIH often reveals coexisting autoimmune disorders, either in the patient or in first-degree relatives. A positive family history of AIH, especially among first-degree relatives, represents a significant risk factor for disease development.[9] Initial laboratory evaluation should include measurement of total IgG, as well as IgA and IgM, since an isolated elevation of IgG is observed in the vast majority of cases. In patients presenting with an acute or fulminant course, this IgG elevation may be absent, suggesting that hypergammaglobulinemia is likely a consequence of hepatic inflammation rather than a primary pathogenic factor, supporting the understanding that AIH is primarily a T cell–mediated disorder rather than one directly driven by autoantibodies. [9]

Nonetheless, the detection of autoantibodies remains a key element of the diagnostic workup. Interpretation can be challenging, as results are influenced by laboratory techniques and the rigor of testing.[10] The most commonly detected autoantibodies in AIH are antinuclear antibodies (ANA) and anti-smooth muscle antibodies (SMA), both of which can also be present in other conditions and, at lower titers, in healthy individuals, particularly in older adults. Depending on local testing availability, initial screening is typically performed using immunofluorescence on rodent tissue sections for ANA, SMA, anti-mitochondrial antibody (AMA), and liver kidney microsomal (LKM) antibodies, supplemented by ELISA or immunoblot assays for soluble liver antigen/liver–pancreas (SLA/LP) antibodies.[11] In pediatric patients or in cases where AIH is suspected despite negative conventional autoantibodies, additional testing may be indicated, including assays for anti-liver cytosol type 1, LKM, double-stranded DNA (dsDNA) antibodies, and immunofluorescence for anti-neutrophil cytoplasmic antibodies.[11]

Many laboratories have transitioned from rodent tissue to Hep2 cell lines for ANA immunofluorescence, which provide greater sensitivity and typically yield approximately twofold higher titers. This difference must be accounted for when interpreting results, and titers are often halved when applied in AIH scoring systems.[10] The substitution of immunofluorescence with ELISA for ANA and SMA detection, commonly performed in the United States, remains controversial and has only been formally evaluated for AIH diagnostic accuracy in a single study.[10] In that study, ELISA demonstrated superior sensitivity and specificity for anti-SMA, which primarily targets F-actin in AIH, but performed less effectively than immunofluorescence for ANA detection. [10,11]

While the majority of autoantibodies in AIH are relatively nonspecific and thus offer limited diagnostic utility, two antibody specificities demonstrate high predictive value: anti-SLA/LP and anti-dsDNA antibodies. Anti-SLA/LP is detected in approximately 15% of AIH patients and is highly specific for the disease. Rarely, anti-SLA/LP may be identified in patients with primary biliary cholangitis (PBC); in such instances, they usually indicate a variant overlap syndrome (PBC/AIH), reflecting at least partial AIH features [12]. Anti-dsDNA antibodies, classically associated with systemic lupus erythematosus (SLE), are present in approximately 20% of AIH patients, typically in conjunction with elevated ANA levels. SLE can coexist with AIH, SLE rarely involves the liver or causes hepatitis. Therefore, histologic evidence of hepatitis together with the presence of anti-dsDNA antibodies can be considered supportive of an AIH diagnosis.[5]

Histological Assessment

Role of Liver Biopsy in Autoimmune Hepatitis

The increasing availability of noninvasive techniques for assessing chronic liver disease has led to a decline in the use of liver biopsy. Nevertheless, in AIH, liver biopsy continues to play a pivotal role in patient management [13]. It remains indispensable for establishing the diagnosis and for providing clinically relevant information on disease activity, remission, or progression during therapy [13]. In patients with persistently negative autoantibodies, liver biopsy is crucial for identifying so-called seronegative AIH, a variant that typically demonstrates a favorable response to corticosteroid treatment [13]. The detection of cirrhosis on

histologic examination has important therapeutic implications, as it may influence both the choice and dosage of immunosuppressive agents and guide surveillance strategies for long-term hepatic complications. Baseline histologic assessment is also relevant for future therapeutic decision-making, given that patients with AIH receiving immunosuppression may subsequently develop other forms of liver disease. Moreover, histologic features observed at presentation may carry prognostic significance, being associated with the risk of progressive fibrosis or cirrhosis, liver-related mortality, or the need for transplantation, and may also help predict treatment response [13]. Current clinical practice guidelines issued by the European Association for the Study of the Liver (EASL) [14], the American Association for the Study of Liver Diseases (AASLD) [15], and various national societies uniformly recommend liver biopsy as a mandatory component for the diagnosis of AIH. For optimal diagnostic accuracy, the biopsy specimen should meet established adequacy criteria, with a recommended minimum length of 1.5 cm and inclusion of at least 6–8 portal tracts, preferably obtained using a 16-gauge or larger needle [14]. The pathology report should document the pattern of inflammation and key diagnostic features, as well as include grading of necroinflammatory activity using Ishak's modified Histological Activity Index and staging of fibrosis and architectural remodeling according to a validated scoring system. The most recent EASL guidelines further emphasize the importance of categorizing histologic findings as likely, possible, or unlikely AIH [14]. Beyond its diagnostic utility, liver biopsy is essential in the differential diagnosis of AIH, as it may reveal an alternative cause of liver injury, identify coexisting liver diseases, or demonstrate features suggestive of overlap syndromes with primary biliary cholangitis or primary sclerosing cholangitis. After the diagnosis is established, liver biopsy may also be used to assess treatment response and, in selected cases, to inform decisions regarding the intensification or withdrawal of immunosuppressive therapy. In routine clinical practice, however, repeat biopsy to confirm remission is generally reserved for patients in whom treatment discontinuation is being considered [16]. This approach is justified because some individuals with complete biochemical remission may still exhibit ongoing necroinflammation or unrecognized progression to cirrhosis on histology, and premature withdrawal of immunosuppression may be harmful. The 2025 EASL clinical practice guidelines acknowledge that robust evidence and prospective data supporting routine liver biopsy prior to treatment cessation are limited; therefore, patient preferences and priorities should be incorporated into shared decision-making [14]. Repeat liver biopsy may also be warranted in cases of disease relapse, suboptimal therapeutic response, or emerging biochemical features of cholestasis with suspicion of an AIH overlap syndrome [14].

Typical Histopathological Features

AIH demonstrates a wide spectrum of histologic manifestations. Although several features have historically been considered characteristic, none are pathognomonic because similar findings may occur in other liver diseases. Moreover, the histologic appearance of AIH may evolve during the clinical course of the disease and in response to treatment [17,18]. Traditionally, the combination of interface hepatitis, hepatocellular rosette formation, and emperipolesis was regarded as "typical histology" according to the 2008 International AIH Group simplified diagnostic criteria [19]. However, these findings are not specific and mainly reflect hepatocellular injury and regenerative activity of diverse etiologies. Current understanding recognizes that the most common histologic pattern in AIH corresponds to nonspecific chronic hepatitis, which may occur with or without accompanying lobular activity [20]. According to the recent consensus recommendations of the International AIH Pathology Group, the likelihood of a histologic diagnosis of AIH in the native liver is determined by the pattern and severity of liver injury [21].

Main Histopathologic Features

Portal inflammation is a central feature of AIH and is present in nearly all cases. The inflammatory infiltrate within portal tracts is typically composed predominantly of lymphocytes, histiocytes, and plasma cells, with occasional neutrophils and eosinophils [22,18]. A key manifestation is interface hepatitis, characterized by extension of inflammatory infiltrates beyond the limiting plate into the periportal parenchyma. This process results in hepatocellular injury and necrosis, which in severe cases may progress to bridging necrosis involving adjacent portal tracts or central veins. Although interface hepatitis can occur in various forms of chronic hepatitis, greater severity of this lesion favors AIH.

Plasma cells have long been regarded as a hallmark of AIH and, when prominent, may support the diagnosis. However, they may be absent in up to 30% of biopsies from patients with AIH and therefore their absence does not exclude the disease [22,17]. Clusters of more than five plasma cells have been proposed as a practical definition to improve interobserver reproducibility, although the optimal threshold remains

uncertain.16 Immunohistochemically, IgG-positive plasma cells predominate in AIH, whereas IgM-positive cells are more typical for primary biliary cholangitis (PBC); however, the diagnostic utility of the IgG/IgM ratio remains controversial [23-26]. Lymphocyte apoptosis within portal tracts has also been suggested as a feature associated with untreated AIH and correlates with the degree of inflammatory activity [27].

Lobular inflammation is common and varies in severity from scattered necroinflammatory foci to confluent or bridging necrosis. Hepatocyte injury may result in architectural disorganization, hepatocellular ballooning, and apoptotic bodies. Regenerative changes are frequently observed, including thickened hepatocellular trabeculae and rosette formation.[22,17,18] Emperipolesis, defined as the presence of inflammatory cells within hepatocyte cytoplasm, is another frequently reported finding and may be present in a substantial proportion of biopsies.[22,28] Although these features are no longer considered specific for AIH, their presence correlates with disease activity and severity.[17,20] Aggregates of Kupffer cells may be present in more severe cases, and Kupffer cells containing hyaline globules—resulting from ingestion of excess immunoglobulins secreted by plasma cells—have been reported more frequently in AIH than in other forms of chronic hepatitis.[20,29]

Additional Histopathologic Features

Centrilobular injury, also referred to as central perivenulitis, is characterized by mononuclear inflammatory infiltrates surrounding central veins with or without associated hepatocellular necrosis. It has been described in approximately 18%–29% of liver biopsies from patients with AIH, typically in association with portal or periportal inflammation and often during acute disease exacerbations [30-33]. Rarely, centrilobular injury may represent the only histologic abnormality and has been proposed as a possible early manifestation of AIH prior to the development of portal inflammation [4]. However, similar changes can also occur in other conditions, including drug-induced liver injury and viral hepatitis [35,36].

Bile duct injury is another relatively common finding in AIH and may complicate the differential diagnosis with cholestatic liver diseases such as PBC or primary sclerosing cholangitis (PSC). Destruction of interlobular bile ducts has been reported in a minority of cases, while lymphocytic cholangitis may occur across a wide range of frequencies [37,38]. These biliary changes are generally considered secondary to intense portal inflammation and do not exclude the diagnosis of AIH [18,38,39]. Ductular reaction, representing proliferation of hepatic progenitor cells forming periportal ductular structures, is also frequently observed and correlates with inflammatory activity, bile duct injury, and fibrosis [37].

Cholestasis is uncommon in AIH, although mild hepatocellular or canalicular cholestasis may occur in cases with acute presentation and marked lobular inflammation [22,17]. In early disease stages, chronic cholestatic features such as periportal copper deposition or keratin-7–positive intermediate hepatocytes may raise suspicion of overlap with PBC or PSC, whereas in advanced fibrosis or cirrhosis these findings are generally regarded as secondary nonspecific phenomena [22,17,39].

Granulomas may be observed in a minority of AIH cases, usually as poorly formed aggregates, whereas well-formed epithelioid granulomas are rare and more typical of PBC or overlap syndromes [22,40]. Microgranulomas composed of small macrophage clusters are associated with prominent lobular inflammation. In addition, multinucleated giant cells may occur as a nonspecific response to hepatocellular injury. Although giant cell hepatitis is more common in neonates, post-infantile giant cell hepatitis in adults is rare; when present, AIH represents the most frequently reported underlying etiology [41,42].

Risk Factors for Autoimmune Hepatitis

Genetic predisposition.

Evidence from genetic analyses indicates that susceptibility to AIH is partly determined by polymorphisms within the human leukocyte antigen (HLA) locus, which encodes the major histocompatibility complex (MHC). The substantial contribution of HLA-encoded genes to disease susceptibility has been confirmed in the largest genome-wide association study conducted in AIH to date [43]. Importantly, the distribution of HLA genotypes associated with AIH varies across ethnic populations and geographic regions [44].

In adult populations from Europe and North America, predisposition to type 1 AIH-1 is most strongly associated with the HLA-DR3 (HLADRB1*0301) and HLA-DR4 (HLADRB1*0401) alleles. These variants encode heterodimers characterized by a lysine residue at position 71 of the DRB1 chain and the hexameric amino acid motif LLEQKR located at positions 67–72 [45,46]. In contrast, studies conducted in Japan, Argentina, and Mexico have identified susceptibility linked to HLADRB1*0405 and HLADRB1*0404 alleles. These variants encode arginine instead of lysine at position 71 while retaining the shared LLEQ-R motif

present in HLADRB1*0401 and HLADRB1*0301 [47]. The presence of basic amino acids—lysine or arginine—at position 71 within the LLEQ-R sequence may therefore be critical for disease susceptibility, potentially facilitating the binding of autoantigenic peptides complementary to this motif. [48]

Epidemiological studies consistently demonstrate a pronounced female predominance in AIH. Independent of disease subtype, women account for approximately 75–80% of affected individuals, a pattern that parallels the distribution observed in many other autoimmune conditions.[49]

Intestinal Barrier Function in Liver Diseases

The intestinal epithelium serves as the primary barrier that maintains intestinal compartmentalization and protects the host from enteric microorganisms. Impairment of this barrier contributes to the pathogenesis of liver disorders as well as other systemic diseases. [50] The intestinal barrier comprises physical, immunological, and microbial components. The physical barrier is formed by the epithelial layer and the overlying mucus, with epithelial integrity maintained by intercellular structures known as tight junctions (TJs).[51] Commensal microbiota support barrier function through multiple mechanisms.[52] Under physiological conditions, goblet cells continuously secrete mucins to sustain the mucus layer. Additionally, commensal organisms activate pattern recognition receptors, such as toll-like receptors (TLRs), on intestinal cells, which stimulates the production of mucins and antimicrobial peptides (AMPs).[53] Many commensal bacteria generate short-chain fatty acids, including butyrate, through fermentation of dietary fiber; among its various functions, butyrate has been shown to support TJ integrity.[54]

When the intestinal barrier is compromised, even normally beneficial bacteria can provoke inflammatory responses and contribute to organ damage.[55] Increased intestinal permeability allows microbe-associated molecular patterns (MAMPs, also known as pathogen-associated molecular patterns [PAMPs]) to translocate into the systemic circulation, eliciting immune activation. Gut-derived PAMPs, such as lipopolysaccharides and microbial RNAs, may reach the liver via the portal vein, triggering hepatic inflammation and fibrosis, often mediated by TLR4 signaling.[56-58]

Multiple, incompletely understood mechanisms contribute to intestinal barrier disruption. These include physical injury, exposure to toxins such as alcohol, TJ disruption, altered epithelial stem cell turnover, and changes in mucus composition.[59,60] Recent studies highlight a strong association between gut microbiome dysbiosis, intestinal permeability, and autoimmune responses.[61] However, the precise molecular pathways linking these phenomena remain largely unresolved. Novel analytical approaches are emerging to identify microbial-derived molecular factors that influence intestinal barrier function.

Microbiota and Immune Dysregulation

In a large case–control study conducted in China, Wei et al. investigated the gut microbiome in steroid-naïve patients with AIH.[62] Compared with healthy controls, patients with AIH exhibited significantly reduced microbial diversity and a distinct compositional profile characterized by depletion of obligate anaerobic taxa, including *Faecalibacterium*, alongside expansion of the genus *Veillonella*. Notably, the species *Veillonella dispar* demonstrated a positive correlation with serum aspartate aminotransferase levels and the degree of hepatic inflammation.[62]

In a cross-sectional German cohort of AIH patients receiving immunosuppressive therapy, Liwinski et al. partially corroborated the principal findings reported by Wei et al., including global alterations in microbiota composition, decreased biodiversity, reduced relative abundance of beneficial anaerobic species such as *Faecalibacterium prausnitzii*, and overrepresentation of *Veillonella*.[63] Additionally, an increased relative abundance of facultative anaerobic genera, including *Streptococcus* and *Lactobacillus*, was observed. A distinctive observation in this study was a marked depletion of the genus *Bifidobacterium*, which was strongly associated with failure to achieve biochemical remission of hepatic inflammation. Importantly, the authors demonstrated that gut microbial alterations in AIH appear to be disease-specific and that AIH can be reliably distinguished from primary biliary cholangitis (PBC) on the basis of microbiota composition.[63]

Another study from China by Ren et al. confirmed the overall reduction in fecal microbial diversity among AIH patients compared with healthy individuals.[64] While the increased relative abundance of *Veillonella* was replicated, this study reported a divergent finding, namely an increased relative abundance of *Faecalibacterium* in AIH patients, in contrast to prior reports.[64]

The oral microbiome has recently emerged as a novel area of investigation in microbiota research. One study demonstrated a significantly higher prevalence of the genus *Veillonella* and a reduced prevalence of the genera *Streptococcus* and *Fusobacterium* in the oral cavity of AIH patients compared with healthy controls.[65]

Although the accumulating body of evidence is promising, the heterogeneity and, in some instances, inconsistency of findings underscore the need for direct comparative analyses across large, internationally diverse cohorts to validate disease-specific microbial signatures in AIH, independent of dietary patterns and geodemographic variables. Furthermore, comprehensive investigations employing shotgun metagenomic sequencing and integrative functional approaches—such as metagenomic functional profiling, metatranscriptomics, proteomics, and metabolomics—remain unavailable in AIH populations. These methodologies may reveal a substantially more complex microbial landscape than that inferred from 16S rRNA gene sequencing alone. To date, no studies have systematically evaluated the virome or mycobiome in AIH. In addition, characterization of the intestinal mucosa-associated microbiome is lacking and may provide a more complete understanding of AIH-associated microbial alterations. [66]

Conclusions

AIH remains a complex and heterogeneous liver disease that poses significant diagnostic and therapeutic challenges. Its variable clinical presentation, ranging from asymptomatic disease to acute liver failure, together with the lack of a single definitive diagnostic marker, necessitates a comprehensive and integrated approach combining clinical, serological, and histopathological data. Liver biopsy continues to play a pivotal role, not only in establishing the diagnosis but also in assessing disease severity, guiding treatment decisions, and evaluating therapeutic response.

Although substantial progress has been made in understanding the immunopathogenesis of AIH, including the role of T-cell–mediated immune dysregulation and genetic susceptibility, many aspects of disease initiation and progression remain unclear. Increasing attention has been directed toward the gut–liver axis, with growing evidence suggesting that intestinal barrier dysfunction and microbiota alterations may contribute to immune activation and hepatic inflammation.

The rising incidence and prevalence of AIH, particularly among older individuals, underscore the need for heightened clinical awareness and improved diagnostic strategies. Future research integrating immunological, genetic, and microbiome-based approaches holds promise for refining disease classification, identifying novel biomarkers, and developing more targeted and individualized therapies.

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