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Liver transplantation for autoimmune hepatitis: a single-center experience in Portugal

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ABSTRACT

Background: Autoimmune hepatitis (AIH) is a complex disease of anomalous immune response against liver tissue which can present as type 1, type 2, and overlap syndrome. Transplantation is the main surgical treatment, with heterogenous outcomes and common later recurrence. No evaluation of the Portuguese reality is available, so the aim of this study is to evaluate clinical, laboratorial and transplantation data of AIH and its post-transplant recurrence at our reference center, in order to improve patient management and approach towards avoiding AIH recurrence.

Methods: Thirty-eight AIH transplanted patients at our center from 27/05/1995 to 31/07/2018 were retrospectively studied regarding demographic and clinical features, immunosuppression, treatment and outcomes.

Results: AIH was more frequent in female than male (3.2:1) and the interval between symptoms onset and transplantation was on average 42±52.97 months (type 1 AIH: 26±45.81 months, type 2 AIH: 24±33.94 months and overlap: 76±56.39). The recurrence of AIH post-transplant was observed in 23.7% (9/38). The most common presentation was chronic hepatitis (44.7%) along with other autoimmune extrahepatic diseases, namely inflammatory bowel disease (10.8%). At the end of the follow-up, 68.4% of patients were alive, 32.7% experienced recurrence in the first five years of follow-up, most interestingly with a higher recurrence in those under cyclosporin A (versus tacrolimus) therapy (p=0.034). Additionally, rejection was also associated with a higher recurrence rate (p=0.016).

Conclusions: AIH is a rare cause for liver transplantation, with a high recurrence rate (23.7%). Rejection and tacrolimus immunosuppression seem to predispose to disease recurrence.

Keywords: Autoimmune hepatitis; Liver transplantation; Recurrent autoimmune hepatitis; immunosuppression.

RESUMO

Introdução: A hepatite autoimune (HAI) é uma doença complexa de resposta imune anômala contra o tecido hepático, que pode se apresentar como tipo 1, tipo 2 e síndrome de sobreposição. O transplante é o principal tratamento cirúrgico, com desfechos heterogêneos e recidiva tardia comum. Não existe avaliação da realidade portuguesa, pelo que o objetivo deste estudo é avaliar os dados clínicos, laboratoriais e de transplante da HAI e a sua recorrência pós-transplante no nosso centro de referência, para melhorar o tratamento e evitar a recorrência da HAI.

Métodos: Trinta e oito pacientes transplantados da AIH em nosso centro, de 27/05/1995 a 31/07/2018, foram estudados retrospetivamente quanto a características demográficas e clínicas, imunossupressão, tratamento e resultados.

Resultados: A HAI foi mais frequente no sexo feminino que no masculino (3,2: 1) e o intervalo entre o início dos sintomas e transplante foi em média 42 ± 52,97 meses (HAI tipo 1: 26 ± 45,81 meses, HAI tipo 2: 24 ± 33,94 meses e sobreposição: 76 ± 56,39). A recorrência de AIH pós-transplante foi observada em 23,7% (9/38). A apresentação mais comum foi hepatite crônica (44,7%), juntamente com outras doenças autoimunes extra-hepáticas, nomeadamente, a doença inflamatória intestinal (10,8%). No fim do seguimento, 68,4% dos pacientes estavam vivos, 32,7% apresentaram recidiva nos primeiros cinco anos de seguimento, curiosamente com maior recorrência naqueles sob terapia com ciclosporina A (versus tacrolimus) (p = 0,034). Além disso, a rejeição também foi associada a uma maior taxa de recorrência (p = 0,016).

Conclusões: A HAI é uma causa rara de transplante hepático, com alta taxa de recorrência (23,7%). A rejeição e a imunossupressão do tacrolimus parecem predispor à recorrência da doença.

Palavras-chave:

Hepatite autoimune; Transplante hepático; Hepatite autoimune recorrente; imunossupressão

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LIST OF ABBREVIATIONS

6MP - 6-mercaptopurine

6TG - 6-thioguanine

AIH – Autoimmune hepatitis

AMA - Anti-mitochondrial antibodies

ANA – Antinuclear antibodies

AST - Aspartate aminotransferase

AZA – Azathioprine

EASL - European Association for the Study of Liver

HAV – Hepatitis A virus

HBV – Hepatitis B virus

HCV – Hepatitis C virus

IgG - Immunoglobulin G

LKM1 - Liver kidney microsomal type 1

LT – Liver transplantation

MELD - Model for End-Stage Liver Disease

MMF - Mycophenolate mofetil

pANCA - Perinuclear anti-neutrophil cytoplasmic antibodies

PBC - Primary biliary cirrhosis

PSC - Primary sclerosing cholangitis

SMA - Smooth muscle antibodies

SLA/LP - Soluble liver antigen/liver-pancreas

Th - Helper T cell

TMPT - Thiopuridine methyl-transferase

UC - Ulcerative colitis

ULN – Upper limit of normal

US – ultrasound

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INTRODUCTION

Autoimmune hepatitis (AIH) is a complex disease of anomalous immune response against liver tissue, being the result of interaction between genetics, immune system, and environmental factors(1). It is characterized by a triad of interface hepatitis with lymphoplasmacytic infiltration, hypergammaglobulinemia and various circulating autoantibodies(2). Currently, its diagnosis is challenging since requires ruling out other chronic liver diseases that may have resembling clinical features(3). AIH usually has a good response to immunosuppressive therapy, but in 10-20% of patients there is a progression for cirrhosis and end-stage liver disease requiring liver transplantation(4). Following liver transplantation, acute allograft rejection and relapse of AIH occurs on a significant percentage of patients(5).

In this study, we evaluate retrospectively all cases of AIH patients submitted to liver transplant (n=38) since the beginning of the liver transplant at our center, in 1995 until 2018 and its recurrence in the graft. We evaluate the clinical presentation, the interval between symptoms and transplantation, the immunosuppressive therapies and the outcomes (rejection, recurrence and survival).

Epidemiology

Autoimmune hepatitis has a global distribution with reported cases in all ethnic groups, ages and genders(6-8). There is a female to male ratio of 3,6 to 1. It's associated to a higher prevalence in north American and northern European white persons with high frequency of HLA-DRB1*03 and HLA-DRB1*04(9). It is responsible for 4 to 6% of adult liver transplantations in Europe and United States(10).

Etiology and physiopathology

As many autoimmune diseases, currently it is believed that the cause of AIH results from a complex interaction between an environmental trigger, individual's genetic predisposition and the immune system(11). There is a clear association between the human leukocyte antigens (HLA)-DR3 and HLA-DR4 and AIH(9). Different triggers have been identified, such as viruses – measles virus, hepatitis A, hepatitis B, hepatitis C and Epstein's-Barr virus(12-17) – drugs – diclofenac, methyldopa, oxyphenisatin, nitrofurantoin and minocycline(18) – and toxins. The precise mechanisms are still unknown.

The strongest immunopathology mechanism hypothesis for AIH is the epitope mimicry, in which there is presentation of an environmental trigger with homologies of the host antigens that leads to bystander activation of resting autoreactive T lymphocytes(19). This will cause a cross-reaction and, subsequently, a loss of self-

tolerance, which provokes an immunopathologic response and, therefore, an immune reaction against the host tissue(19). The time between exposure and onset of disease can be long, and the presence of the trigger agent is no need for the perpetuation of the disease(20). The CD4+ or helper T (Th) cell is the main effector cell, being its activation the first step of the pathogenic pathway(21).

Another proposed pathogenic mechanism for AIH is the epitope spreading or exposure of hidden autoantigens due to hepatocellular injury(19). This will lead to presentation of an autoantigen via MHC and costimulatory molecules which will produce several cytokines, leading to differentiation of uncommitted CD4 T-helper cells (Th0) to Th1-cells (secretion of interferon-γ), Th-17 (secretion of IL-17) or Th2 (secretion of IL-13, IL-4), indicating that all these effector cells could be involved in AIH pathogenesis. This can be explained by a decrease in the immunoregulatory mechanisms. This decrease is not fully understood, but current data point in a malfunction of regulatory T-cells, particularly CD4+CD25+FOXP3+ T-cells(22).

Clinical features

Autoimmune hepatitis has a fluctuate and heterogeneous behaviour. To simplify, clinicians categorize it in 3 major groups. It can present as: i) an acute icteric hepatitis, which can be a challenge to diagnosis, since its clinical and biochemical parameters are compatible with an acute viral hepatitis(23); ii) an oligosymptomatic mild to moderate chronic disease, with clinical presentation similar to other forms of chronic hepatitis(24); or iii) asymptomatic and therefore unrecognized disease, which later on will mostly be diagnosed as “cryptogenic” cirrhosis(25, 26). The most common symptom is ready fatigability (86%) while the most common physical finding is hepatomegaly (78%). Jaundice is found in 69% of patients(25, 26).

As many immune-mediated diseases, AIH is usually presented with other autoimmune disorders. Ranging between 4 to 44%, patients present other concurrent conditions, being autoimmune thyroiditis, Grave’s disease and rheumatoid arthritis the most common(27). Thyroid disorders and rheumatoid arthritis are usually associated with younger patients, whereas ulcerative colitis or autoimmune haemolysis are more common in older patients(27). It is important to notice that these conditions may obscure the diagnosis of AIH, so clinicians must be aware of these associations(27). Plus, it’s crucial to mention that AIH is associated with negative effect on health-related quality of life(28).

Laboratory features

The major biochemical markers in AIH are serum aminotransferase activity, with a predominance of aspartate aminotransferase (AST), bilirubin concentrations, serum alkaline phosphatase and hypergammaglobulinemia. Both aminotransferase activity and bilirubin concentration are usually elevated (over 50 times upper normal limits), while serum alkaline phosphatase can be normal or elevated(29). Nevertheless, aminotransferase and bilirubin levels vary from individual and over time, so are not considered good methods for AIH diagnosis(30). Specifically in AIH, hypergammaglobulinemia has a disproportional increase of immunoglobulin G (IgG), which may be elevated even if the total concentration of immunoglobulins are normal(29).

Serologic tests are paramount for the diagnosis of AIH, and should always be done when there is clinical, laboratory and/or histological suspicion. The three major autoantibodies in this disease are antinuclear antibodies (ANA), smooth muscle antibodies (SMA) and liver kidney microsomal type 1 antibody (anti-LKM1)(31). If negative and clinical suspicion remains, anti-soluble liver antigen/liver-pancreas antibodies (anti-SLA/LP) may be useful to search(32). Both ANA and SMA are not disease nor organ specific, but its detection together constitutes a good serologic exam, with high sensibility and specificity(33). Anti-LKM is positive usually when both ANA and SMA are negative, being strongly associated with paediatric patients. Anti-SLA/LP has a very high specificity for AIH (99%) but are not present in most patients. It has been proven to have prognostic value(34).

Other serologic markers of AIH are atypical pANCA(32), anti-actin(35), anti-asialoglycoprotein receptor(36) and anti-liver cytosol type 1(37).

Histology

Contrary to some autoimmune diseases, there is no pathognomonic histological features in AIH. The most common histological feature in AIH is interface (para-septal or periportal) hepatitis with a lymphoplasmacytic necro-inflammatory infiltrate(38). Other histological findings are infiltration of plasma cells, rosettes, necrosis of pyknotic (apoptotic) cells, ballooning degeneration of hepatocytes (39%) and emperipolesis (penetration of one cell into and through a larger cell)(38, 39). Presence of fibrosis alongside these findings is typical in AIH. Development to advanced fibrosis and cirrhosis may occur rapidly in AIH(23, 24). Acute severe (fulminant) has a proposed histologic diagnosis – lymphoplasmacytic infiltration around the central vein with hepatocyte drop-out or necrosis, which is usually associated with lymphoid aggregates and plasma cell infiltration(40).

Diagnosis

Clinical criteria

Due to the absence of pathognomonic features in AIH, diagnosis of this disease requires the combination of symptoms and physical exam, laboratory findings, serology and histology(30) (table I). It is necessary to exclude other hepatic diseases such as viral hepatitis, alcoholic hepatitis, drug-induced hepatitis, hemochromatosis, Wilson disease, α1-antitrypsin deficiency, primary biliary cirrhosis, and primary sclerosing cholangitis(30). Laboratory findings should include abnormal elevation of serum gamma globulin and/or IgG levels(30). Serology compatible with AIH includes positive antinuclear antibodies (ANA), smooth muscle antibodies (SMA) or antibodies to liver-kidney microsome type 1 (LKM1)(30), which helps classify between type 1 or type 2 AIH. On the histologic examination, interface hepatitis should be present, which may be associated with plasma cell infiltration, hepatocyte rosettes and/or centrilobular necrosis(30). According to the presence of etiologic factors or the degree of immune reactivity, it can be differentiate between definite or probable AIH(30).

Table I - Diagnostic algorithm for autoimmune hepatitis(30)

Presenting features	Acute, chronic or acute severe onset Serum AST-to-alkaline phosphatase ratio > 3 Elevated serum gamma globulins, IgG and/or AST	
Necessary exclusions	AMA - Normal cholangiogram if UC or cholestasis Ceruloplasmin normal Normal α1-antritrypsin phenotype Transferrin saturation inferior to 45% Non-alcoholic or drug-induced hepatitis HAV, HBV and HCV markers negative	
Histological findings	Interface hepatitis with or without plasma cell infiltration, hepatocyte rosettes and/or centrilobular necrosis	
Diagnosis	**Definite AIH** Gamma globulins and/or IgG superior to 1,5 ULN ANA, SMA or anti-LKM1 superior or equal to 1:80 No drugs or blood products Alcohol intake inferior to 25g/day	**Probable AIH** Gamma globulins and/or IgG inferior to 1,5 ULN ANA, SMA or anti-LKM1 inferior or equal to 1:40 Previous drugs or blood products Alcohol intake inferior to 50g/day Nonstandard liver-related autoantibodies present
Type	**Type 1 AIH** **SMA and/or ANA +**	**Type 2 AIH** **Anti-LKM1 +**

Scoring criteria

The purpose of scoring systems is for research and should not be used as a discriminative diagnostic index, but rather to ensure a uniform evaluation of each single

patient. The original scoring system (table II) was developed during 1992 with an update at 1999(30). A simplified score (table III) was developed during 2008, and uses only 5 categories: autoantibodies, viral disease, immunoglobulin level, histologic findings and pre-treatment aggregate score(41). Both scores have already been compared, having the simplified score a better specificity (90 vs 73%) and predictability (92 vs 82%), while the original scoring system has better sensitivity (100 vs 95%)(41).

Table II – Revised original scoring system for the diagnosis of autoimmune hepatitis - Adapted from(30).

Category	**Variable**	**Score**
Gender	Female	+2
Alk Phos: AST (or ALT) ratio	>3	-2
	<1,5	+2
Gamma globulin or IgG level	>2,0 times ULN	+3
	1,5-2,0 times ULN	+2
	1,0-1,5 times ULN	+1
	<1,0 times ULN	0
ANA, SMA or anti-LKM1 titres	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
AMA	Positive	-4
Viral markers of active infection	Positive	-3
	Negative	+3
Drug history	Yes	-4
	No	+1
Alcohol	<25 g/day	+2
	>60 g/day	-2
HLA	DR3 or DR4	+1
Concurrent immune disease	Thyroiditis, UC, synovitis, others	+2
Other autoantibodies	Anti-SLA, actin, LC1, pANCA	+2
Histologic features	Interface hepatitis	+3
	Plasmacytic infiltrate	+1
	Rosettes	+1
	None of the above	-5
	Biliary changes	-3
	Other features	-3
Treatment response	Complete	+2
	Relapse	+3
Pre-treatment score		
Definite diagnosis		>15
Probable diagnosis		10-15
Post-treatment score		
Definite diagnosis		>17
Probable diagnosis		12-17

Table III – Simplified scoring system for the diagnosis of autoimmune hepatitis, adapted from(41).

Category	Variable	Score
Autoantibodies		
ANA or SMA	1:40	+1
Anti-LKM1	≥1:80	+2
	≥1:40	+2
Anti-SLA	Positive	+2
Immunoglobulin level		
IgG (times above upper limit of normal)	>1	+1
	>1,1	+2
Histologic findings		
Morphologic features (relation to autoimmune hepatitis)	Compatible	+1
	Typical	+2
Viral disease		
Absence of viral hepatitis	No viral markers	+2
Pre-treatment of viral hepatitis		
Definite diagnosis		≥7
Probable diagnosis		6

Classification and variants

Type 1 autoimmune hepatitis:

Type 1 AIH is characterized by a specific serology and a different behaviour from other variants. It is associated with the detection of antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA). Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) can be present up to 90% in type 1 AIH, contrary to type 2, in which is rarely present. It occurs at any age or gender and has a female-to-male ratio of 3,5:1. Extrahepatic autoimmune diseases are commonly associated such as autoimmune thyroiditis or type 1 diabetes(42). It usually presents an abrupt onset of symptoms, but it can present itself in fulminant form(43).

Type 2 autoimmune hepatitis

Type 2 AIH is strongly associated with antibodies against liver kidney microsome type-1 (LKM1) (44). Contrary to type 1, most patients are children (2 to 14 years), even though it can appear on adults. Concurrent autoimmune diseases are present in many cases, having already been associated with type 1 diabetes *mellitus(45)*and vitiligo(46), for example. Acute and fulminant onset are possible presentations(47).

Nonclassical presentations

Asymptomatic patients

AIH can have an asymptomatic presentation in 34-45% of cases, with compatible histological characteristics of AIH (25, 26). This group can have histological improvement without any medical intervention, but it's rare and most of the cases incomplete(48). Progression to cirrhosis and liver failure are possible(48). Due to its aggressive inflammatory activity, it justifies treatment, independently of symptoms or severity. This is stated by comparing untreated patients with mild asymptomatic AIH and treated patients with severe symptomatic AIH. The 10-year survival is superior in the treated group (67 vs 98%)(49).

Acute severe (fulminant) presentation

While constituting only 6% of cases, being aware of this variant is important due to its severity (40). This presentation represents one of the most arduous diagnosis, for different reasons. It can have a clinical behaviour similar to an acute viral or toxic hepatitis (47), with marked serum aminotransferase elevations and histologic changes such as massive hepatic necrosis, plasma cell infiltration, centrilobular necrosis and lymphoid follicles. Unlike other types, typical histologic and laboratory findings are usually absent. IgG serum is normal in 25-39% of cases, with ANA absent or weakly positive.

Autoantibody-negative autoimmune hepatitis

This variant is classified when patients with negative ANA, SMA and anti-LKM1 antibodies fulfil the international criteria of the diagnosis of AIH(50). Representing 13% of cases(51), they have epidemiological, clinical, laboratory and histological features similar with classic AIH, and HLA frequencies compatible to AIH as well. It's important in these cases to exclude other diseases that can mimic AIH behaviour (Wilson disease, celiac-related liver diseases and drug-induced liver disease)(50). 15-20% of the cases can be reclassified when evaluated for atypical pANCA and anti-SLA antibodies(50).

Drug-induced autoimmune-like hepatitis

Representing 9% of patients diagnosed with AIH, there are several drugs associated with this variant – minocycline and nitrofurantoin (most common – 90% of cases), methyldopa, di-hydralazine, halothane, tienilic acid and oxiphenistatin(52). This variant usually presents with an acute onset, with jaundice (69%) and hypersensitivity features (fever, rash and eosinophilia – 15-20%)(52). Histologic findings include classic AIH features and eosinophils. Biopsy can find features than can favour drug-induced injury – portal neutrophils and cholestasis – or favour AIH – portal and intra-acinar plasma cells, hepatocyte rosettes and emperipolesis(39).

Overlap syndromes

Overlap syndromes are define by having a predominant phenotype of AIH, with secondary features of cholestatic liver disease (for this classification, AIH must be the principal phenotype)(53). Findings of cholestatic diseases are separated in three different groups: primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and cholestatic syndrome with indistinguishable form (AMA-negative PBS or small-duct PSC)(53).

Treatment

Standard treatment

The AIH treatment has two main objectives: induce and maintain remission of the disease activity at a clinical, laboratory and histological level(10). Currently, the goal of the treatment is a complete normalization of transaminases, bilirubin and IgG levels (10).

Being diagnosed with AIH implies, in most of the cases, the necessity of treatment with immunosuppressive drugs. Nevertheless, it is important to note that some patients may only require monitoring. This clinical option can be weighted if the patient has a low-grade histologic activity, absence of higher fibrosis stages, and enough liver function. Unfortunately, only a minority of patients fulfil these circumstances, and this option is always based on individual circumstances and the preferences of the patient(54).

The standard treatment is based on two pharmacological steps. First, we induce remission with a steroid-based treatment. Second, we maintain that remission with a thiopurine-based treatment. For induction of remission, the most used option is prednisolone between 0,5 to 1 mg/kg/day, and constantly wean over time. For maintenance of remission, the first option is azathioprine 1-1,5 mg/kg/day, in monotherapy or combined with prednisolone, in low-dose(55). Current European (EASL) guidelines advice to introduce azathioprine 2 weeks after starting steroids, to help differentiate between azathioprine-induced hepatotoxicity and primary non-response, when faced with persistent pathological levels of liver enzymes(56).

As an alternative to prednisolone to induce remission, European Association for the Study of Liver (EASL) proposes budesonide with a starting dose of 9 mg/day, which has proved better results in both remission and less side effects. However, according to a recent survey, this option was not used by a single expert hepatologist, due to the greater and successful experience with other treatments(57). It is also important to mention that, due to being a drug that requires hepatic first pass effect, it is contraindicated in patients with cirrhosis(58).

The duration of immunosuppression is far from being defined, but current studies show patients with AIH demanding a life-long treatment, being the duration of 24 months

the minimum required for a stable biochemical remission(56). In addition, 80% of patients relapse after a 3-year period of discontinuation(59). Unluckily, a life-long treatment with immunosuppressive drugs is the main responsible for the mortality of AIH, so the possibility of therapy withdrawal should be weighted(56). Due to a poor correlation between biochemical and histological activity, many centres propose the use of a follow-up biopsy before the discontinuation of the treatment(56).

Alternative and second line treatments

Patients intolerant to standard treatment

A significant minority of patients (10-20%) do not respond to standard treatment. In this group of patients there are two main drugs we can choose. If the patient has normal levels of thiopuridine methyl-transferase (TMPT), thiopurine 6-mercaptopurine (6MP) is a good alternative in patients with intolerance to azathioprine (a prodrug of 6MP)(60). The thiopurine metabolism creates two final metabolites: 6-methyl mercaptopurine – associated with hepatotoxicity – and 5-thioguanine (6TG) – mediates the therapeutic immunosuppressive effect as well as side effects like myelosuppression. Close monitoring to detect bone marrow toxicity is crucial. In patients with insufficient levels of thiopuridine methyltransferase, mycophenolate mofetil is an option(61).

Patients with insufficient response to standard treatment

When faced with insufficient response to immunosuppressive treatment, the most logical approach should be to increase the dosage of drugs. Nevertheless, this should be balanced with the patient own risk, considering the side effects, infectious complications and the high-risk of progression to cirrhosis in this group of patients.

Calcineurin inhibitors are commonly used in these situations. Both cyclosporine and tacrolimus have improved immunological and biochemical parameters (10). A recent study showed MMF had a better response (56,5%) than tacrolimus (34%) in this group of patients(62).

Patients with acute and severe presentation

Current knowledge of AIH treatment is not enough to have a defined algorithm for severe manifestations, with controversy in the use of corticosteroids. Currently, it has been agreed that high dose of steroid treatment can be beneficial in most cases. The optimal dose, response criteria and the best timing for liver transplantation, still, remain undefined. When there is no response to the treatment, patients with severe AIH should be evaluated for liver transplantation(63).

Patients with paediatric-onset disease

AIH in adults and in children have different presentations. In children, autoimmune sclerosing cholangitis (ASC) – overlap syndrome and primary sclerosing

cholangitis - is present up to 50% of patients with AIH. This justifies the alteration of the therapeutic regimen. The treatment algorithm is similar to classic AIH, with addiction of ursodeoxycholic acid at a daily dose of 15-20 mg/day(64). It is important to mention that paediatric-onset disease has a higher percentage of liver transplantation, recurrent flares and death(65).

Prognosis

Different clinical aspects can predict the prognosis of AIH patients. A score of 12 or more points at presentation by MELD score identifies 97% of patients that will fail conventional glucocorticoid therapy and will require liver transplantation or die of liver failure(42). Positivity of anti-SLA at presentation unquestionably defines that those patients will relapse after glucocorticoid withdraw(66). Response to initial medical treatment also helps to predict worse prognosis. Patients who, after 12 months of standard treatment, fail to achieve normal or near normal levels at laboratory tests or liver histology have higher frequency of liver transplantation (15 vs 2%) and progression to cirrhosis (54 vs 18%)(67). Curiously, young adults have a higher frequency of treatment failure than older people (20 vs 7%)(68).

AIH and tumour surveillance

A recent meta-analysis proved there is an incidence rate of hepatocellular carcinoma in AIH patients of 3,06 per 1000 patients by year, being almost all cases associated with cirrhosis. Furthermore, the incidence rises to 10,07 per 1000 patients by year in whom already have cirrhosis, being lower than cirrhosis associated with viral hepatitis(69). However, AIH-cirrhosis cases might benefit from hepatocellular carcinoma surveillance. Abdominal US every 6 months should be considered. Due to the duration of immunosuppressive therapy, 5% of patients with AIH have extrahepatic malignancies.

Liver transplantation

Liver transplantation is the current main surgical treatment for AIH, representing 4% of all liver transplantations done in Europe and North America(10). It should be considered in AIH patients who either develop end-stage liver disease despite treatment or develop fulminant hepatic failure (with encephalopathy) without corticoid response. It’s associated with a 5 and 10-years survival of 83 and 75% respectively with graft survival of 92%. Relapse happens on 20-36% of patients(19, 70). De novo AIH occurs in 6-10% of patients(71).

After liver transplantation, immunosuppression is required. Most common pharmacological regime used in these situations is calcineurin inhibitor together with AZA

or mycophenolate and corticosteroids, though there is still no optimal regimen established(72).

After LT, patients grafted for AIH are at a higher risk for acute and chronic rejection. Due to this, reduction of immunosuppressive regimen should be performed cautiously. Two risk factors have been identified for chronic rejection: young age of transplantation and moderate to severe acute rejection(73).

Recurrent autoimmune hepatitis

Recurrence of primary disease after liver transplantation has become a prime issue for both clinicals and researchers. Recurrence is defined by the reappearance of the primary disease in the allograft. Due to longer survival and increasing success of liver transplantation, the recurrence of the primary disease has become a fundamental aspect of morbidity and mortality post transplantation. Criteria for diagnosis of recurrent AIH is still not established, though the hallmark is interface hepatitis with or without plasma cells that can include other aspects such as acute lobular hepatitis with focal hepatocyte necrosis, pseudo-rosetting of hepatocytes or acidophil bodies with lymphoplasmacytic cells(74). Current evidence shows that the role of autoantibodies for diagnosing recurrent AIH are still uncertain(5). Risk factors for recurrent AIH following LT are not fully understood. Treatment of recurrent AIH is usually empiric, based on restarting or intensifying corticosteroid therapy, add new immunosuppressive drugs or reinforce adherence to medical therapy(75).

***De novo* autoimmune hepatitis**

De novo autoimmune hepatitis is characterized by a clinical syndrome mimicking AIH in patients transplanted for nonautoimmune liver disease(71). These patients undergo liver transplantation and feature afterwards high levels of IgG, serum autoantibodies and histological findings compatible to classic AIH(71). The standard treatment for *de novo* autoimmune hepatitis are based on corticosteroids.

MATERIALS AND METHODS

In this retrospective study we evaluate the demographic and clinical characteristics of patients with autoimmune hepatitis submitted to liver transplantation in Centro Hospitalar Universitario do Porto. The data was collected by analysis of clinical files between 27/05/1995 to 31/07/2018, and all of them were anonymized. For each patient, we collected demographic and clinical data including bilirubin, AST, ALT, alkaline phosphatase, gamma-glutamyl-transferase, albumin, creatinine, prothrombin time and IgG. The statistical treatment was performed using SPSS, version 24. Categoric variables were compared with qui-square/Fisher test, while numeric ones were with t-student test. Inclusion criteria involve patients undergoing liver transplantation in the context of proven autoimmune hepatitis.

RESULTS

Demographic and clinical data of the 38 AIH liver transplanted patients are summarized in Table IV. For analysis, patients were separated according the clinical presentation of the AIH in 3 subgroups: type 1, type 2 and overlap. Most patients were female (76.3%). Only 20% of the subgroup “overlap” and 23.7% of the subgroup type 1 AIH were male. The mean age of patients at AIH diagnosis was 43 ± 14 years old, ranged from 17 to 63 years old. The 2 patients with type 2 developed the disease earlier in life than the others (18 versus 39 years old for overlap and 47 years old for type 1 AIH).

Interval between symptoms and liver transplantation was extremely variable, ranged from 0 to 144 months, with a standard deviation of 52.97 months. The interval was lower for type 2 AIH, although this group had only 2 patients.

The most prevailing presentation of AIH was chronic hepatitis, in 44.7% of cases, 42.3% of the cases in type 1 AIH group and 60% in overlap group. The second most common presentation was acute hepatitis with 28.9% of cases and in the remaining 26.3% the disease presented as acute liver failure. About one third (30.5%) of the patients had autoimmune associated diseases, most commonly inflammatory bowel disease, present in 10.5% of the cases.

Serum laboratory data at the time of liver transplantation were analyzed (Table V). Value of total bilirubin was on average 10.2 mg/dl, ranged from 0.4 to 31.1 mg/dl and the subgroup with the highest average concentration of total bilirubin (11.4 mg/dl) was the type 1 AIH. The mean AST and ALT levels were 234 U/L and 246 U/L respectively, with type 2 AIH having both AST and ALT highest mean concentration, 563 U/L and 480 U/L respectively. Alkaline phosphatase level was on average 182 U/L and gamma-glutamyl-transferase level was on average 137 U/L. Both alkaline phosphatase and gamma-glutamyl-transferase levels were higher on the overlap group (311 U/L and 264 U/L, respectively). Mean serum albumin level was 3.05 and serum creatinine level was 0.62 (0.10 – 1.52) mg/dl, both parameters showed higher concentrations in type 2 AIH group. Prothrombin time was on average 21.04 seconds, with the highest level observed in type 1 AIH group (24.65) and the lowest in type 2 AIH group (5.85). IgG average was 2002.21, with highest average levels on type 1 AIH with 2135.04. According to Child-Pugh Score, all patients were classified as C at the time of the transplantation.

Concerning the technical aspects of liver transplantation on AIH patients (Table VI), 42.1% of patients were initially immunosuppressed with cyclosporin A, while the rest was immunosuppressed with tacrolimus. The surgical technique used was the piggyback technique in 57.9% and the classic technique in the remaining 42.1% of the cases. Roughly half (52.6%) of all transplantations required blood transfusion while, in contrast, only 10.5% demanded platelet transfusions and 15.8% plasma transfusion. No platelet

or plasma transfusions were required in any patient of the overlap group. In 15.8% of the interventions occurred arterial complications, being the thrombosis of hepatic artery the most frequent. No arterial complications were recorded on overlap group. Only type 1 AIH group had surgical wound complications, in 23.1% of cases. Following liver transplantation, 12 patients died, 7 within 30 day after transplant and the 5 between second and 20th month post-transplant. The death causes were acute liver failures in 3 cases and infection/multi-organic failures in the remaining 9 cases. Twelve patients (31.6%) experienced rejection (26.9% of the type 1 AIH and 50% of the type 2 AIH), 3 of them died. Loss of graft occurred in 34.2% of patients, 38.5% in type 1 AIH and 20% in overlap group.

Autoimmune hepatitis recurred in 9 of 38 patients (23.7%) in the five years following liver transplant. One of the two patients with type 2 AIH group (50%) had recurrence of the disease, followed by overlap group with 4 cases (40%). The lowest percentage of recurrence was observed in type 1 AIH group (15.4%). For comparative analysis (Table 4), the population of this study was separated in two groups – non-recurrent AIH (n=29) and recurrent AIH (n=9). Most patients of both groups were females (79.3% of the non-recurrent group and 66.7% of the recurrent group (p=0.357). Those with recurrent AIH were younger (36.67±12.47 years old) than those without recurrence (45.10±13.67 years old), p=0.108. The presentation clinical picture was similar in both groups with an acute presentation in 55.2% of the non-recurrent AIH group patients and 55.5% of the recurrent AIH group patients, p=0.643. Five of the 29 patients with no recurrence (17.2%) had received a liver from a familial amyloidosis TTR V30M patient (domino transplantation), while no cases were reported on recurrent AIH, p=0.237.

No significant differences were observed between groups reporting mean bilirubin, AST, ALT, alkaline phosphatase, gamma-glutamyl-transferase and creatinine levels (Table VII). Albumin levels were 3.01±0.69 g/dl on non-recurrent AIH and 3.16±0.51 in recurrent group, p=0.562. Prothrombin levels were 20.48±14.82 seconds in non-recurrent AIH versus 22.74±20.23 seconds in recurrent AIH group, p=0.719.

After transplant, rejection was significantly more frequent in those with AIH recurrence (66.7% versus 20.7%, p=0.016). Concerning initial suppression, tacrolimus was used in 88.9% of the AIH recurrent group patients and in 48.3% of non-recurrent AIH group, p=0.034. The rest were immunosuppressed with cyclosporin A. No significant differences were observed in surgical technique between both groups, with classic technique performed on 44.8% of non-recurrent AIH and 33.3% of recurrent AIH, p=0.416. No significant differences were also observed relative to transfusions. There was no record of arterial nor bile duct complications on recurrent AIH group, while 20.7% and 24.1% of non-recurrent AIH patients had experienced arterial complications and bile

duct complications, with p=0.172 and 0.124, respectively. Surgical wounds complications were slightly more frequent in recurrent AIH than in non-recurrent AIH patients (22.2% versus 13.7%, p=0.441).

From the 9 patients with AIH recurrence, 2 were retransplanted and died after the second transplant. The others seven patients have a follow-up of 7 (3-14) years with graft survival after immunosuppression increase. It is unclear which factors predispose to AIH recurrence after liver transplantation. In this study we analyzed the possible influence of several continuous and categorical variables. None of the continuous variables analyzed by Cox regression revealed a significantly influence on recurrence of AIH, namely patient's age (p=0.581), patient's age at time of diagnosis (p=0.267), interval between onset of symptoms and the diagnosis (p=0.535), interval between diagnosis and liver transplantation (p=0.131). Categorical variables analyzed were associated autoimmune diseases (p=0.977, non-significant), presentation symptoms - overlap versus other types (p=0.278, non-significant), gender (p=0.967, non-significant), rejection (p=0.068, almost significant) and immunosuppression - tacrolimus versus cyclosporin A (p=0.034, significant).

Table IV – Demographic and clinical presentation analysis of 38 AIH patients submitted to liver transplant.

	Total (n=38)	**Type 1 (n= 26)**	**Type 2 (n=2)**	**Overlap (n=10)**
Female (%)	29 (76.30%)	19 (73.10%)	2 (100%)	8 (80%)
Age (years)	43 (17-63) ± 14	47 (24-63) ± 11.78	18 (17-19) ± 1.41	39 (20-55) ± 13.74
Interval between symptoms and transplantation (months)	42 (0-144) ± 52.97	26 (0-144) ± 45.81	24 (0-48) ± 33.94	76 (16-132) ± 56.39
Alive (%)	26 (68.4%)	17 (65.4%)	1 (50%)	8 (80%)
Child-Pugh score (C)	0:0:38 (100%)	0:0:26 (100%)	0:0:2 (100%)	0:0:10 (100%)
Mode of presentation				
Acute hepatitis	11 (28.9%)	6 (23.1%)	1 (50%)	4 (40%)
Acute liver failure	10 (26.3%)	9 (34.6%)	1 (50%)	0 (0%)
Chronic hepatitis	17 (44.7%)	11 (42.3%)	0 (0%)	6 (60%)
Autoimmune diseases present				
Associated autoimmune diseases	10 (30.5%)	6 (22.2%)	1 (50%)	3 (30%)
Inflammatory bowel disease	4 (10.5%)	1	1	2
Hashimoto disease	2 (5.2%)	2		
Type 1 diabetes	1 (2.6%)	1		
CREST syndrome	1 (2.6%)			1
Dermatomyositis	1 (2.6%)	1		
Pernicious anemia	1 (2.6%)	1		

Table V – Laboratorial data at transplantation time (time 0) of 38 AIH transplants

	Total (n=38)	**Type 1 (n= 26)**	**Type 2 (n=2)**	**Overlap AIH (n=10)**
Total Bilirubin (mg/dL)	10.2 (0.4-31.1) ± 8.9	11.3 (1.0-29.5) ± 9.0	9.9 (3.7-16.1) ± 8.7	7.5 (0.4-31.1) ± 8.9
AST (U/L)	234 (33-1938) ± 346	248 (248 -1938) ± 408	563 (519 - 608) ± 63	135 (39 - 215) ± 60
ALT (U/L)	246 (23 -2276) ± 429	289 (23 -2276) ± 511	480 (333 - 627) ± 207	94 (43 -159) ± 39
Alkaline phosphatase (U/L)	182 (45-529) ± 129	139 (45-328) ± 63	56 (48 -65) ± 12	311 (95 - 529) ± 165
Gamma-glutamyl-transferase (U/L)	137 (5-712)± 171	94 (21-389) ± 88	21 (5-37) ± 22	264 (15 - 712) ± 262
Albumin (g/dL)	3.0 (1.6-4.2) ± 0.64	2.9 (1.6-4.1) ± 0.6	3.5 (2.9-4.1) ± 0.8	3.2 (2.3-4.2) ± 0.7
Creatinine (mg/dL)	0.62 (0.1-1.52) ± 0.29	0.64 (0.1-1.52) ± 0.32	0.8	0.56 (0.2-0.84) ± 0.22
Prothrombin time (seconds)	21.0 (4.6-75.7) ± 16.1	24.7 (5.5-75.7) ± 18.2	5.9 (4.6-7.1) ± 1.8	15.4 (6.3-27.7) ± 6.3
IgG (mg/dL)	2002 (657-4874) ± 983	2135 (1080-4874) ± 1036	1920	1871 (657-3517) ± 859

Table VI – Transplant and post-transplant data

	Total (n=38)	**Type 1 (n= 26)**	**Type 2 (n=2)**	**Overlap AIH (n=10)**
Initial immunosuppression				
Cyclosporin A	16 (42.1%)	13 (50%)	1 (50%)	2 (20%)
Tacrolimus	22 (57.9%)	13 (50%)	1 (50%)	8 (80%)
Surgical technique				
Classic	16 (42.1%)	10 (38.5%)	1 (50%)	5 (50%)
Piggyback	22 (57.9%)	16 (61.5%)	1 (50%)	5 (50%)
Transfusions				
Blood transfusions	20 (52.6%)	15 (57.7%)	1 (50%)	4 (40%)
Platelet transfusion	4 (10.5%)	4 (15.4%)	0 (0%)	0 (0%)
Plasma transfusion	6 (15.8%)	6 (23.1%)	0 (0%)	0 (0%)
Complications				
Arterial complications	6 (15.8%)	5 (19.2%)	1 (50%)	0 (0%)
Bile duct complications	7 (18.4%)	5 (19.2%)	0 (0%)	2 (20%)
Surgical wound complications	6 (15.8%)	6 (23.1%)	0 (0%)	0 (0%)
Post-transplant events				
Rejection after transplantation	12 (31.6%)	7 (26.9%)	0 (0%)	5 (50%)
Loss of graft	13 (34.2%)	10 (38.5%)	1 (50%)	2 (20%)

Table VII -Comparative analysis between non-recurrent AIH vs recurrent AIH groups.

Type of AIH	**Non-recurrent AIH n=29**	**Recurrent AIH n=9**	**P<0.05**
Female (%)	23 (79.3%)	6 (66.7%)	0.357
Age (years)	45.10±13.67	36.67±12.47	0.108
Mode of presentation			
Acute presentation	16 (55.2%)	5 (55.5%)	0.643
Chronic presentation	13 (44.8%)	4 (44.4%)	
Sequential transplantation	5 (17.2%)	0 (0%)	0.237
Associated autoimmune diseases	13/29 (44.8%)	3/9 (33.3%)	
Patients Alive (%)	66.5%	77.8%	
Serum laboratory data			
Total bilirubin (mg/dL)	9.58±8.75	12.14±9.63	0.461
AST (U/L)	247±394.4	197.6±130.9	0.717
ALT (U/L)	265.7±484.5	187±194.8	0.493
Alkaline phosphatase (U/L)	194.1±136.2	146.9±103	0.349
Gamma-glutamyl-transferase (U/L)	140.2±187.4	129.9±121.2	0.880
Albumin (g/dL)	3.01±0.69	3.16±0.51	0.562
Creatinine (mg/dL)	0.61±0.32	0.64±0.22	0.769
Prothrombin time (seconds)	20.48±14.82	22.74±20.23	0.719
Post- transplantation			
Rejection	6 (20.7%)	6 (66.7%)	**0.016**
Initial immunosuppression			
Tacrolimus	14 (48.3%)	8 (88.9%)	**0.034**
Cyclosporin A	15 (51.7%)	1 (11.1%)	
Surgical technique			
Classic	13 (44.8%)	3 (33.3%)	0.416
Piggyback	16 (55.2%)	6 (66.7%)	
Transfusions			
Blood Transfusion	16 (55.2%)	4 (44.4%)	0.427
Platelet transfusion	4 (13.7%)	0 (0%)	0.322
Complications			
Arterial complications	6 (20.7%)	0 (0%)	0.172
Bile duct complications	7 (24.1%)	0 (0%)	0.124
Surgical wound complications	4 (13.7%)	2 (22.2%)	0.441

Analysis of Kaplan-Meier curves showed a decrease of patient survival in the first 1-2 years, stabilizing at 0.7 cumulative survival. In terms of graft survival, there was a rapid decline on the first year, stabilizing at 0.7 cumulative survival at the third year. Recurrence of AIH occurred during the first five years, with a cumulative survival of 0.6. Those who had rejection developed recurrence early (Figure 1). Tacrolimus is a predisposing factor to recurrence (Figure 2), however it is important to notice that despite their significance, the size of the sample is small with only 9 recurrences.

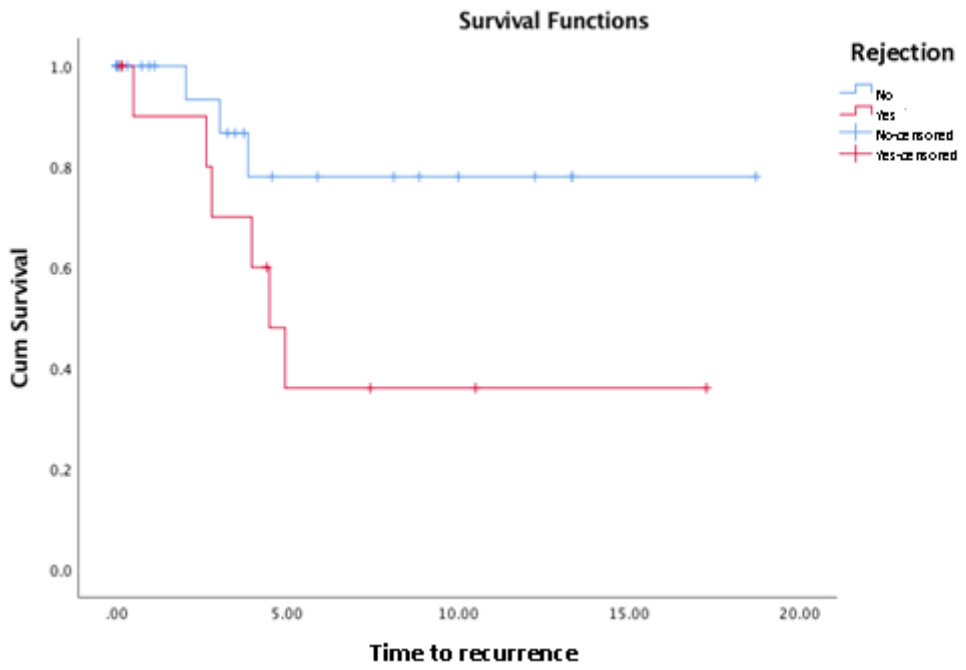

Figure 1. Survival analysis by Kaplan-Meier. Patients who suffered an episode of rejection had a greater percentage of and lesser time to recurrence (p=0.016).

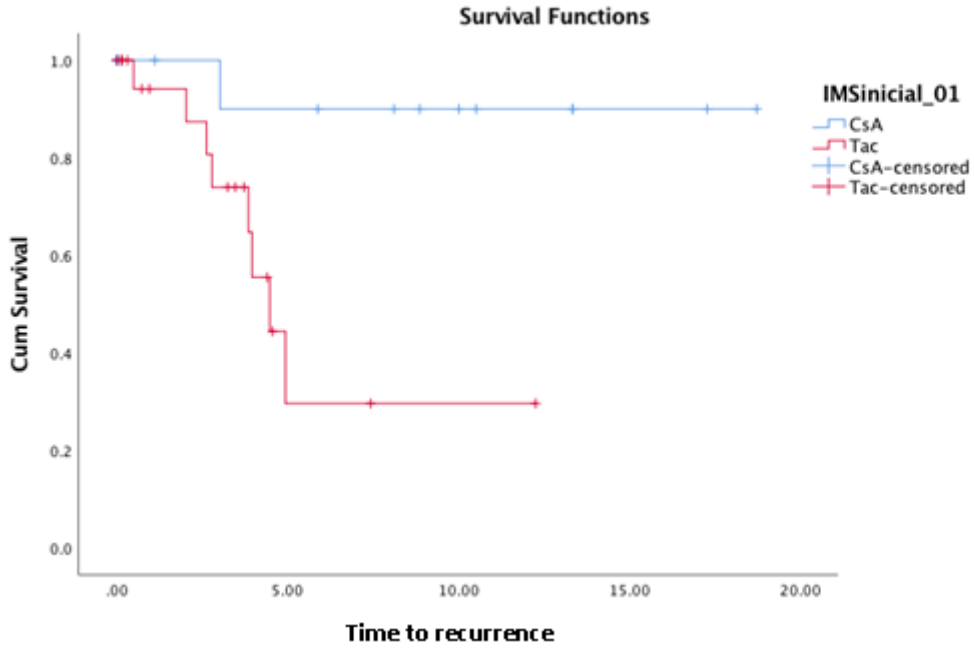

Figure 2. Survival analysis by Kaplan-Meier. Tacrolimus treatment is a predisposing factor to recurrence of AIH, both occurring in greater percentage and in less time (p=0.034)

DISCUSSION

AIH is a destructive inflammatory process that, despite immunosuppressive therapy after liver transplantation, it can recur in the graft. Since it is a rare cause for liver transplant, most of the studies already performed evaluate long time periods with relatively few cases detected. In our study, during 23 years of liver transplantation, 38 patients were transplanted due to AIH, and 9 (23.7%) recurred. In our center, liver biopsy is only performed when clinically indicated, and previously studies in centers with the same biopsy protocol, the AIH recurrence was identified in 24-33%(76-78) similar to our results. Our patients were mainly women, with female/male of 3.2:1, similar to other studies (F/M of 3.6:1)(27, 79). However, in type 1 AIH group, this ratio was 2.7:1, lower than the previously reported of 3.5:1(27, 79). About patients' age, the mean age was 43 years old, similar to other studies. The 2 patients from type 2 AIH group had 17 and 19 years, far younger than the other patients, further showing the distinction of this group(80). As expected, the overlap syndrome patients exhibited more varied ages, showing its heterogeneous onset. The interval between symptoms and liver transplantation was on average 42 months, with overlap group associated with a longer and heterogenous clinical evolution, on average 76 months. The most common presentation was chronic hepatitis, with 44.7% of patients, which is supported by current data(81). However, it's worth noticing that almost all acute liver failure occurred on type 1 AIH group which, adding up the smallest interval between symptoms and liver transplantation of 26 months, demonstrates the more aggressive nature of type 1 AIH group. In our study, 30.5% of patients had other associated autoimmune diseases, which can contribute to misdiagnosis by hiding typical symptoms of AIH. Most common autoimmune diseases present was inflammatory bowel disease (10.8%), followed by Hashimoto disease (5.2%), two well connected autoimmune diseases with AIH(19, 27, 70, 76, 79, 82, 83). However, to the best of our knowledge, it's for the first time recorded a patient who had both AIH and CREST syndrome. According to the previously described, AIH responds well to immunosuppressive therapy, and it this estimated that only 10% require transplant due to end-stage liver disease or steroid unresponsive disease(84). Following transplant, 5-year patient survival has been described as near 80%(85). In our study, 68.4% of patients are currently alive, which confirm the favorable outcome of liver transplantation in this setting.

Laboratory data reinforces the clinical heterogeneous nature of AIH, supported by its range of presentation, from acute hepatic failure to chronic hepatitis. Total bilirubin levels ranged from 0.44 (anicteric) to 31.10 (concentration enough to cause hepatic encephalopathy). AST and ALT also showed variable results, (AST ranging from 33 to 1938 and ALT ranging from 23 and 2276), with mean ALT levels higher than AST levels,

which goes against current data of AIH, which frequently presents with a higher level of AST. It's also worth mentioning that overlap group had a significant lower level of AST and ALT. On the contrary, it had a higher level of alkaline phosphatase and gamma-glutamyl-transferase, which is comprehensible considering the pathophysiology of overlap syndrome, which correlates with inflammation of both liver and bile ducts. Hypo albuminemia was observed in all groups, on average 3.05 g/dl, and prothrombin time was longer than normal, on average 16.06 seconds, suggesting that the severity of inflammation of hepatic tissue leads to chronic diminished liver production. Type 1 AIH had lower levels of albumin and higher levels of prothrombin time, confirming its aggressive nature, as previously mentioned. Serum creatinine level was, on average, 0.62 mg/dl (maximum of 1.52 mg/dl) and no case of hepatorenal syndrome was diagnosed. IgG levels were, on average, 2002.21±983.10 mg/dl, high but extremely variable.

Considering the immunosuppressive therapy, all patients were treated with calcineurin inhibitors – cyclosporin A or tacrolimus. Even though no optimal immunosuppressive regimen has been established, current data supports an immunosuppression regime of calcineurin inhibitors associated with azathioprine and mycophenolate with or without corticosteroids. This divergency can be explained by the interval of these study (between 1995 and 2018) where many shifts between immunosuppression have happened. Patients treated with tacrolimus have more AIH recurrences than those treated with cyclosporin A (p= 0.034), suggesting a harmful effect of tacrolimus. This effect was previously reported by Ayata G et al(80). Cyclosporin A is an immunomodulator specific of T cells, while tacrolimus inhibits indirectly T cells, by reducing the production of IL-2. The greater effectiveness of cyclosporin A s in preventing AIH recurrence may be due to its specificity of action on T cells. Surgical technique was similar between those with and without AIH recurrence (p=0.416). Surgical wound complications, mainly infection, and arterial thrombosis were observed in 15.8% of patients, like the percentage observed in liver transplantation in general, which suggest that AIH is not a risk factor for these complications and no differences were observed in those with AIH recurrence.

Patients with AIH recurrence were younger than those without recurrence (36.67±12.47 versus 45.10±13.67 years old, p=0.108), suggesting that a bigger population could potentially give a statistically significant difference on this variable. The presentation of the AIH was similar (p=0.643), that showcases that recurrence of AIH seems independent of its presentation and clinical behavior. Serum laboratory data had no difference between all variables studied, being alkaline phosphatase the variable with lowest p(p=0.349).

An important fact is that 66.7% of those with AIH recurrence had at least an episode of rejection compared to 20.7% of those without recurrence, a statistically significant difference of rejection after transplantation between both groups (p=0.016). Rejection seems to be a predictor of AIH recurrence, suggesting an incomplete immunosuppression and/or a more aggressive disease variant.

In conclusion, AIH is a rare indication for liver transplant. Its recurrence affected 23,7% of our patients and seems be predict by rejection. Immunosuppressive therapy also seems to influence the post-transplant evolution with tacrolimus associated to more AIH recurrence. The size of our population, with only 38 patients, is a limitation of this study. Larger studies are needed to define more risk factors and early biomarkers for AIH recurrence.

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Is cyclosporin A the key for recurrent autoimmune hepatitis?

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Abstract:	Background Autoimmune hepatitis (AIH) is a complex disease of anomalous immune response against liver tissue which can present as type 1, type 2, and overlap syndrome. Transplantation is the main surgical treatment, with heterogenous outcomes and common later recurrence. No evaluation of the Portuguese reality is available, so the aim of this study is to evaluate clinical, laboratorial and transplantation data of AIH and its post-transplant recurrence at our reference center, in order to improve patient management and approach towards avoiding AIH recurrence. Methods Thirty-eight AIH transplanted patients at our center from 27/05/1995 to 31/07/2018 were retrospectively studied regarding demographic and clinical features, immunosuppression, treatment and outcomes. Results AIH was more frequent in female than male (3.2:1) and the interval between symptoms onset and transplantation was on average 42±52.97 months (type 1 AIH: 26±45.81 months, type 2 AIH: 24±33.94 months and overlap: 76±56.39). The recurrence of AIH post-transplant was observed in 23.7% (9/38). The most common presentation was chronic hepatitis (44.7%) along with other autoimmune extrahepatic diseases, namely inflammatory bowel disease (10.8%). At the end of the follow-up, 68.4% of patients were alive, 32.7% experienced recurrence in the first five years of follow-up, most interestingly with a higher recurrence in those under cyclosporin A (versus tacrolimus) therapy (p=0.034). Additionally, rejection was also associated with a higher recurrence rate (p=0.016). Conclusions AIH is a rare cause for liver transplantation, with a high recurrence rate (23.7%). Rejection and tacrolimus immunosuppression seem to predispose to disease recurrence.

Is cyclosporin A the key for recurrent autoimmune hepatitis?

Abstract

Background: Autoimmune hepatitis (AIH) is a complex disease of anomalous immune response against liver tissue which can present as type 1, type 2, and overlap syndrome. Transplantation is the main surgical treatment, with heterogenous outcomes and common later recurrence. No evaluation of the Portuguese reality is available, so the aim of this study is to evaluate clinical, laboratorial and transplantation data of AIH and its post-transplant recurrence at our reference center, in order to improve patient management and approach towards avoiding AIH recurrence.

Methods: Thirty-eight AIH transplanted patients at our center from 27/05/1995 to 31/07/2018 were retrospectively studied regarding demographic and clinical features, immunosuppression, treatment and outcomes.

Results: AIH was more frequent in female than male (3.2:1) and the interval between symptoms onset and transplantation was on average 42±52.97 months (type 1 AIH: 26±45.81 months, type 2 AIH: 24±33.94 months and overlap: 76±56.39). The recurrence of AIH post-transplant was observed in 23.7% (9/38). The most common presentation was chronic hepatitis (44.7%) along with other autoimmune extrahepatic diseases, namely inflammatory bowel disease (10.8%). At the end of the follow-up, 68.4% of patients were alive, 32.7% experienced recurrence in the first five years of follow-up, most interestingly with a higher recurrence in those under cyclosporin A (versus tacrolimus) therapy (p=0.034). Additionally, rejection was also associated with a higher recurrence rate (p=0.016).

Conclusions: AIH is a rare cause for liver transplantation, with a high recurrence rate (23.7%). Rejection and tacrolimus immunosuppression seem to predispose to disease recurrence.

Introduction

Autoimmune hepatitis (AIH) is a disease present worldwide[1-4], with a female/male ratio of 3,6:1[5,6] and a peak incidence in the 40s to 50s[6-8]. It's clinical presentation ranged from asymptomatic disease to acute icteric hepatitis or mild to moderate chronic disease[9], without pathognomonic features[10]. AIH is classified as type 1, type 2 or overlap syndrome. The type 1, more frequent in female (3,5:1)[5], usually had an abrupt presentation[11], occurs at any age and is associated with ANA or SMA positive[12]. The type 2 is more frequent in children (2-14 years), associated with anti-LKM1[12] and it can present an acute and fulminant onset. The overlap syndrome is characterized by predominant features of AIH, with a secondary phenotype of cholestatic liver disease[12]. AIH is usually associated with other autoimmune diseases, being autoimmune thyroiditis, Grave's disease and rheumatoid arthritis the most frequent[1,5,13-15]. Liver transplantation for AIH is indicated for those with fulminant hepatic failure (with encephalopathy) non corticoid responsive or in case of evolution to end-stage liver disease, despite treatment[16]. The most common immunosuppressive regimen is based on calcineurin inhibitor, azathioprine or mycophenolate and corticosteroids[17]. After liver transplantation, there is a higher risk for acute and chronic rejection[18], and the disease recurrence affects 20-36% of patients[19-21].

In this study, we evaluate retrospectively all cases of AIH patients submitted to liver transplant (n=38) since the beginning of the liver transplant at our center, in 1995 until 2018 and its recurrence in the graft. We evaluate the clinical presentation, the interval between symptoms and transplantation, the immunosuppressive therapies and the outcomes (rejection, recurrence and survival).

Materials and Methods

In this retrospective study we evaluate the demographic and clinical characteristics of patients with autoimmune hepatitis submitted to liver transplantation in Centro Hospitalar Universitario do Porto. The data was collected by analysis of clinical files between 27/05/1995 to 31/07/2018, and all of them were anonymized. For each patient, we collected demographic and

clinical data including bilirubin, AST, ALT, alkaline phosphatase, gamma-glutamyl-transferase, albumin, creatinine, prothrombin time and IgG. The statistical treatment was performed using SPSS, version 24. Categoric variables were compared with qui-square/Fisher test, while numeric ones were with t-student test. Inclusion criteria involve patients undergoing liver transplantation in the context of proven autoimmune hepatitis.

Results

Demographic and clinical data of the 38 AIH liver transplanted patients are summarized in Table 1. For analysis, patients were separated according the clinical presentation of the AIH in 3 subgroups: type 1, type 2 and overlap. Most patients were female (76.3%). Only 20% of the subgroup “overlap” and 23.7% of the subgroup type 1 AIH were male. The mean age of patients at AIH diagnosis was 43 ± 14 years old, ranged from 17 to 63 years old. The 2 patients with type 2 developed the disease earlier in life than the others (18 versus 39 years old for overlap and 47 years old for type 1 AIH).

Interval between symptoms and liver transplantation was extremely variable, ranged from 0 to 144 months, with a standard deviation of 52.97 months. The interval was lower for type 2 AIH, although this group had only 2 patients.

The most prevailing presentation of AIH was chronic hepatitis, in 44.7% of cases, 42.3% of the cases in type 1 AIH group and 60% in overlap group. The second most common presentation was acute hepatitis with 28.9% of cases and in the remaining 26.3% the disease presented as acute liver failure. About one third (30.5%) of the patients had autoimmune associated diseases, most commonly inflammatory bowel disease, present in 10.5% of the cases.

Serum laboratory data at the time of liver transplantation were analyzed (Table 2). Value of total bilirubin was on average 10.2 mg/dl, ranged from 0.4 to 31.1 mg/dl and the subgroup with the highest average concentration of total bilirubin (11.4 mg/dl) was the type 1 AIH. The mean AST and ALT levels were 234 U/L and 246 U/L respectively, with type 2 AIH having both AST and ALT highest mean concentration, 563 U/L and 480 U/L respectively. Alkaline

phosphatase level was on average 182 U/L and gamma-glutamyl-transferase level was on average 137 U/L. Both alkaline phosphatase and gamma-glutamyl-transferase levels were higher on the overlap group (311 U/L and 264 U/L, respectively). Mean serum albumin level was 3.05 and serum creatinine level was 0.62 (0.10 – 1.52) mg/dl, both parameters showed higher concentrations in type 2 AIH group. Prothrombin time was on average 21.04 seconds, with the highest level observed in type 1 AIH group (24.65) and the lowest in type 2 AIH group (5.85). IgG average was 2002.21, with highest average levels on type 1 AIH with 2135.04. According to Child-Pugh Score, all patients were classified as C at the time of the transplantation.

Concerning the technical aspects of liver transplantation on AIH patients (Table 3), 42.1% of patients were initially immunosuppressed with cyclosporin A, while the rest was immunosuppressed with tacrolimus. The surgical technique used was the piggyback technique in 57.9% and the classic technique in the remaining 42.1% of the cases. Roughly half (52.6%) of all transplantations required blood transfusion while, in contrast, only 10.5% demanded platelet transfusions and 15.8% plasma transfusion. No platelet or plasma transfusions were required in any patient of the overlap group. In 15.8% of the interventions occurred arterial complications, being the thrombosis of hepatic artery the most frequent. No arterial complications were recorded on overlap group. Only type 1 AIH group had surgical wound complications, in 23.1% of cases. Following liver transplantation, 12 patients died, 7 within 30 day after transplant and the 5 between second and 20th month post-transplant. The death causes were acute liver failures in 3 cases and infection/multi-organic failures in the remaining 9 cases. Twelve patients (31.6%) experienced rejection (26.9% of the type 1 AIH and 50% of the type 2 AIH), 3 of them died. Loss of graft occurred in 34.2% of patients, 38.5% in type 1 AIH and 20% in overlap group.

Autoimmune hepatitis recurred in 9 of 38 patients (23.7%) in the five years following liver transplant. One of the two patients with type 2 AIH group (50%) had recurrence of the disease, followed by overlap group with 4 cases (40%). The lowest percentage of recurrence was observed in type 1 AIH group (15.4%). For comparative analysis (Table 4), the population of this study was separated in two groups – non-recurrent AIH (n=29) and recurrent AIH (n=9). Most patients

of both groups were females (79.3% of the non-recurrent group and 66.7% of the recurrent group (p=0.357). Those with recurrent AIH were younger (36.67±12.47 years old) than those without recurrence (45.10±13.67 years old), p=0.108. The presentation clinical picture was similar in both groups with an acute presentation in 55.2% of the non-recurrent AIH group patients and 55.5% of the recurrent AIH group patients, p=0.643. Five of the 29 patients with no recurrence (17.2%) had received a liver from a familial amyloidosis TTR V30M patient (domino transplantation), while no cases were reported on recurrent AIH, p=0.237.

No significant differences were observed between groups reporting mean bilirubin, AST, ALT, alkaline phosphatase, gamma-glutamyl-transferase and creatinine levels (Table 4). Albumin levels were 3.01±0.69 g/dl on non-recurrent AIH and 3.16±0.51 in recurrent group, p=0.562. Prothrombin levels were 20.48±14.82 seconds in non-recurrent AIH versus 22.74±20.23 seconds in recurrent AIH group, p=0.719.

After transplant, rejection was significantly more frequent in those with AIH recurrence (66.7% versus 20.7%, p=0.016). Concerning initial suppression, tacrolimus was used in 88.9% of the AIH recurrent group patients and in 48.3% of non-recurrent AIH group, p=0.034. The rest were immunosuppressed with cyclosporin A. No significant differences were observed in surgical technique between both groups, with classic technique performed on 44.8% of non-recurrent AIH and 33.3% of recurrent AIH, p=0.416. No significant differences were also observed relative to transfusions. There was no record of arterial nor bile duct complications on recurrent AIH group, while 20.7% and 24.1% of non-recurrent AIH patients had experienced arterial complications and bile duct complications, with p=0.172 and 0.124, respectively. Surgical wounds complications were slightly more frequent in recurrent AIH than in non-recurrent AIH patients (22.2% versus 13.7%, p=0.441).

From the 9 patients with AIH recurrence, 2 were retransplanted and died after the second transplant. The others seven patients have a follow-up of 7 (3-14) years with graft survival after immunosuppression increase. It is unclear which factors predispose to AIH recurrence after liver transplantation. In this study we analyzed the possible influence of several continuous and categorical variables. None of the continuous variables analyzed by Cox regression revealed

a significantly influence on recurrence of AIH, namely patient's age (p=0.581), patient's age at time of diagnosis (p=0.267), interval between onset of symptoms and the diagnosis (p=0.535), interval between diagnosis and liver transplantation (p=0.131). Categorical variables analyzed were associated autoimmune diseases (p=0.977, non-significant), presentation symptoms - overlap versus other types (p=0.278, non-significant), gender (p=0.967, non-significant), rejection (p=0.068, almost significant) and immunosuppression - tacrolimus versus cyclosporin A (p=0.034, significant).

Analysis of Kaplan-Meier curves showed a decrease of patient survival in the first 1-2 years, stabilizing at 0.7 cumulative survival. In terms of graft survival, there was a rapid decline on the first year, stabilizing at 0.7 cumulative survival at the third year. Recurrence of AIH occurred during the first five years, with a cumulative survival of 0.6. Those who had rejection developed recurrence early (Figure 1). Tacrolimus is a predisposing factor to recurrence (Figure 2), however it is important to notice that despite their significance, the size of the sample is small with only 9 recurrences.

Discussion

AIH is a destructive inflammatory process that, despite immunosuppressive therapy after liver transplantation, it can recur in the graft. Since it is a rare cause for liver transplant, most of the studies already performed evaluate long time periods with relatively few cases detected. In our study, during 23 years of liver transplantation, 38 patients were transplanted due to AIH, and 9 (23.7%) recurred. In our center, liver biopsy is only performed when clinically indicated, and previously studies in centers with the same biopsy protocol, the AIH recurrence was identified in 24-33%[22-24], similar to our results. Our patients were mainly women, with female/male of 3.2:1, similar to other studies (F/M of 3.6:1) [5,6]. However, in type 1 AIH group, this ratio was 2.7:1, lower than the previously reported of 3.5:1[5,6]. About patients' age, the mean age was 43 years old, similar to other studies [8-10]. The 2 patients from type 2 AIH group had 17 and 19 years, far younger than the other patients, further showing the distinction of this group[25]. As expected, the overlap syndrome patients exhibited more varied ages, showing

its heterogeneous onset. The interval between symptoms and liver transplantation was on average 42 months, with overlap group associated with a longer and heterogenous clinical evolution, on average 76 months. The most common presentation was chronic hepatitis, with 44.7% of patients, which is supported by current data[18]. However, it's worth noticing that almost all acute liver failure occurred on type 1 AIH group which, adding up the smallest interval between symptoms and liver transplantation of 26 months, demonstrates the more aggressive nature of type 1 AIH group. In our study, 30.5% of patients had other associated autoimmune diseases, which can contribute to misdiagnosis by hiding typical symptoms of AIH. Most common autoimmune diseases present was inflammatory bowel disease (10.8%), followed by Hashimoto disease (5.2%), two well connected autoimmune diseases with AIH[1,5,6,19-22]. However, to the best of our knowledge, it's for the first time recorded a patient who had both AIH and CREST syndrome. According to the previously described, AIH responds well to immunosuppressive therapy, and it this estimated that only 10% require transplant due to end-stage liver disease or steroid unresponsive disease[26]. Following transplant, 5-year patient survival has been described as near 80%[27]. In our study, 68.4% of patients are currently alive, which confirm the favorable outcome of liver transplantation in this setting.

Laboratory data reinforces the clinical heterogeneous nature of AIH, supported by its range of presentation, from acute hepatic failure to chronic hepatitis. Total bilirubin levels ranged from 0.44 (anicteric) to 31.10 (concentration enough to cause hepatic encephalopathy). AST and ALT also showed variable results, (AST ranging from 33 to 1938 and ALT ranging from 23 and 2276), with mean ALT levels higher than AST levels, which goes against current data of AIH, which frequently presents with a higher level of AST. It's also worth mentioning that overlap group had a significant lower level of AST and ALT. On the contrary, it had a higher level of alkaline phosphatase and gamma-glutamyl-transferase, which is comprehensible considering the pathophysiology of overlap syndrome, which correlates with inflammation of both liver and bile ducts. Hypo albuminemia was observed in all groups, on average 3.05 g/dl, and prothrombin time was longer than normal, on average 16.06 seconds, suggesting that the severity of inflammation of hepatic tissue leads to chronic diminished liver

production. Type 1 AIH had lower levels of albumin and higher levels of prothrombin time, confirming its aggressive nature, as previously mentioned. Serum creatinine level was, on average, 0.62 mg/dl (maximum of 1.52 mg/dl) and no case of hepatorenal syndrome was diagnosed. IgG levels were, on average, 2002.21±983.10 mg/dl, high but extremely variable.

Considering the immunosuppressive therapy, all patients were treated with calcineurin inhibitors – cyclosporin A or tacrolimus. Even though no optimal immunosuppressive regimen has been established, current data supports an immunosuppression regime of calcineurin inhibitors associated with azathioprine and mycophenolate with or without corticosteroids. This divergency can be explained by the interval of these study (between 1995 and 2018) where many shifts between immunosuppression have happened. Patients treated with tacrolimus have more AIH recurrences than those treated with cyclosporin A (p= 0.034), suggesting a harmful effect of tacrolimus. This effect was previously reported by Ayata G et al[25]. Cyclosporin A is an immunomodulator specific of T cells, while tacrolimus inhibits indirectly T cells, by reducing the production of IL-2. The greater effectiveness of cyclosporin A s in preventing AIH recurrence may be due to its specificity of action on T cells. Surgical technique was similar between those with and without AIH recurrence (p=0.416). Surgical wound complications, mainly infection, and arterial thrombosis were observed in 15.8% of patients, like the percentage observed in liver transplantation in general, which suggest that AIH is not a risk factor for these complications and no differences were observed in those with AIH recurrence.

Patients with AIH recurrence were younger than those without recurrence (36.67±12.47 versus 45.10±13.67 years old, p=0.108), suggesting that a bigger population could potentially give a statistically significant difference on this variable. The presentation of the AIH was similar (p=0.643), that showcases that recurrence of AIH seems independent of its presentation and clinical behavior. Serum laboratory data had no difference between all variables studied, being alkaline phosphatase the variable with lowest p(p=0.349).

An important fact is that 66.7% of those with AIH recurrence had at least an episode of rejection compared to 20.7% of those without recurrence, a

statistically significant difference of rejection after transplantation between both groups (p=0.016). Rejection seems to be a predictor of AIH recurrence, suggesting an incomplete immunosuppression and/or a more aggressive disease variant.

In conclusion, AIH is a rare indication for liver transplant. Its recurrence affected 23,7% of our patients and seems be predict by rejection. Immunosuppressive therapy also seems to influence the post-transplant evolution with tacrolimus associated to more AIH recurrence. The size of our population, with only 38 patients, is a limitation of this study. Larger studies are needed to define more risk factors and early biomarkers for AIH recurrence.

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Tables

Table 1 – Demographic and clinical presentation analysis of 38 AIH patients submitted to liver transplant.

	Total (n=38)	**Type 1 (n= 26)**	**Type 2 (n=2)**	**Overlap (n=10)**
Female (%)	29 (76.30%)	19 (73.10%)	2 (100%)	8 (80%)
Age (years)	43 (17-63) ± 14	47 (24-63) ± 11.78	18 (17-19) ± 1.41	39 (20-55) ± 13.74
Interval between symptoms and transplantation (months)	42 (0-144) ± 52.97	26 (0-144) ± 45.81	24 (0-48) ± 33.94	76 (16-132) ± 56.39
Alive (%)	26 (68.4%)	17 (65.4%)	1 (50%)	8 (80%)
Child-Pugh score (C)	0:0:38 (100%)	0:0:26 (100%)	0:0:2 (100%)	0:0:10 (100%)
Mode of presentation				
Acute hepatitis	11 (28.9%)	6 (23.1%)	1 (50%)	4 (40%)
Acute liver failure	10 (26.3%)	9 (34.6%)	1 (50%)	0 (0%)
Chronic hepatitis	17 (44.7%)	11 (42.3%)	0 (0%)	6 (60%)
Autoimmune diseases present				
Associated autoimmune diseases	10 (30.5%)	6 (22.2%)	1 (50%)	3 (30%)
Inflammatory bowel disease	4 (10.5%)	1	1	2
Hashimoto disease	2 (5.2%)	2		
Type 1 diabetes	1 (2.6%)	1		
CREST syndrome	1 (2.6%)			1
Dermatomyositis	1 (2.6%)	1		
Pernicious anemia	1 (2.6%)	1		

Table 2 – Laboratorial data at transplantation time (time 0) of 38 AIH transplants

	Total (n=38)	**Type 1 (n= 26)**	**Type 2 (n=2)**	**Overlap AIH (n=10)**
Total Bilirubin (mg/dL)	10.2 (0.4-31.1) ± 8.9	11.3 (1.0-29.5) ± 9.0	9.9 (3.7-16.1) ± 8.7	7.5 (0.4-31.1) ± 8.9
AST (U/L)	234 (33-1938) ± 346	248 (248 -1938) ± 408	563 (519 - 608) ± 63	135 (39 - 215) ± 60
ALT (U/L)	246 (23 -2276) ± 429	289 (23 -2276) ± 511	480 (333 - 627) ± 207	94 (43 -159) ± 39
Alkaline phosphatase (U/L)	182 (45-529) ± 129	139 (45-328) ± 63	56 (48 -65) ± 12	311 (95 - 529) ± 165
Gamma-glutamyl-transferase (U/L)	137 (5-712)± 171	94 (21-389) ± 88	21 (5-37) ± 22	264 (15 - 712) ± 262
Albumin (g/dL)	3.0 (1.6-4.2) ± 0.64	2.9 (1.6-4.1) ± 0.6	3.5 (2.9-4.1) ± 0.8	3.2 (2.3-4.2) ± 0.7
Creatinine (mg/dL)	0.62 (0.1-1.52) ± 0.29	0.64 (0.1-1.52) ± 0.32	0.8	0.56 (0.2-0.84) ± 0.22
Prothrombin time (seconds)	21.0 (4.6-75.7) ± 16.1	24.7 (5.5-75.7) ± 18.2	5.9 (4.6-7.1) ± 1.8	15.4 (6.3-27.7) ± 6.3
IgG (mg/dL)	2002 (657-4874) ± 983	2135 (1080-4874) ± 1036	1920	1871 (657-3517) ± 859

Table 3 – Transplant and post-transplant data

	Total (n=38)	Type 1 (n= 26)	Type 2 (n=2)	Overlap AIH (n=10)
Initial immunosuppression				
Cyclosporin A	16 (42.1%)	13 (50%)	1 (50%)	2 (20%)
Tacrolimus	22 (57.9%)	13 (50%)	1 (50%)	8 (80%)
Surgical technique				
Classic	16 (42.1%)	10 (38.5%)	1 (50%)	5 (50%)
Piggyback	22 (57.9%)	16 (61.5%)	1 (50%)	5 (50%)
Transfusions				
Blood transfusions	20 (52.6%)	15 (57.7%)	1 (50%)	4 (40%)
Platelet transfusion	4 (10.5%)	4 (15.4%)	0 (0%)	0 (0%)
Plasma transfusion	6 (15.8%)	6 (23.1%)	0 (0%)	0 (0%)
Complications				
Arterial complications	6 (15.8%)	5 (19.2%)	1 (50%)	0 (0%)
Bile duct complications	7 (18.4%)	5 (19.2%)	0 (0%)	2 (20%)
Surgical wound complications	6 (15.8%)	6 (23.1%)	0 (0%)	0 (0%)
Post-transplant events				
Rejection after transplantation	12 (31.6%)	7 (26.9%)	0 (0%)	5 (50%)
Loss of graft	13 (34.2%)	10 (38.5%)	1 (50%)	2 (20%)

Table 4 -Comparative analysis between non-recurrent AIH vs recurrent AIH groups.

Type of AIH	**Non-recurrent AIH n=29**	**Recurrent AIH n=9**	**P<0.05**
Female (%)	23 (79.3%)	6 (66.7%)	0.357
Age (years)	45.10±13.67	36.67±12.47	0.108
Mode of presentation			
Acute presentation	16 (55.2%)	5 (55.5%)	0.643
Chronic presentation	13 (44.8%)	4 (44.4%)	
Sequential transplantation	5 (17.2%)	0 (0%)	0.237
Associated autoimmune diseases	13/29 (44.8%)	3/9 (33.3%)	
Patients Alive (%)	66.5%	77.8%	
Serum laboratory data			
Total bilirubin (mg/dL)	9.58±8.75	12.14±9.63	0.461
AST (U/L)	247±394.4	197.6±130.9	0.717
ALT (U/L)	265.7±484.5	187±194.8	0.493
Alkaline phosphatase (U/L)	194.1±136.2	146.9±103	0.349
Gamma-glutamyl-transferase (U/L)	140.2±187.4	129.9±121.2	0.880
Albumin (g/dL)	3.01±0.69	3.16±0.51	0.562
Creatinine (mg/dL)	0.61±0.32	0.64±0.22	0.769
Prothrombin time (seconds)	20.48±14.82	22.74±20.23	0.719
Post- transplantation			
Rejection	6 (20.7%)	6 (66.7%)	**0.016**
Initial immunosuppression			
Tacrolimus	14 (48.3%)	8 (88.9%)	**0.034**
Cyclosporin A	15 (51.7%)	1 (11.1%)	
Surgical technique			
Classic	13 (44.8%)	3 (33.3%)	0.416
Piggyback	16 (55.2%)	6 (66.7%)	
Transfusions			
Blood Transfusion	16 (55.2%)	4 (44.4%)	0.427
Platelet transfusion	4 (13.7%)	0 (0%)	0.322
Complications			
Arterial complications	6 (20.7%)	0 (0%)	0.172
Bile duct complications	7 (24.1%)	0 (0%)	0.124
Surgical wound complications	4 (13.7%)	2 (22.2%)	0.441

Figure legends

Figure 1 - Survival analysis by Kaplan-Meier. Patients who suffered an episode of rejection had a greater percentage of and lesser time to recurrence (p=0.016).

Figure 2 - Survival analysis by Kaplan-Meier. Tacrolimus treatment is a predisposing factor to recurrence of AIH, both occurring in greater percentage and in less time (p=0.034)

Figure

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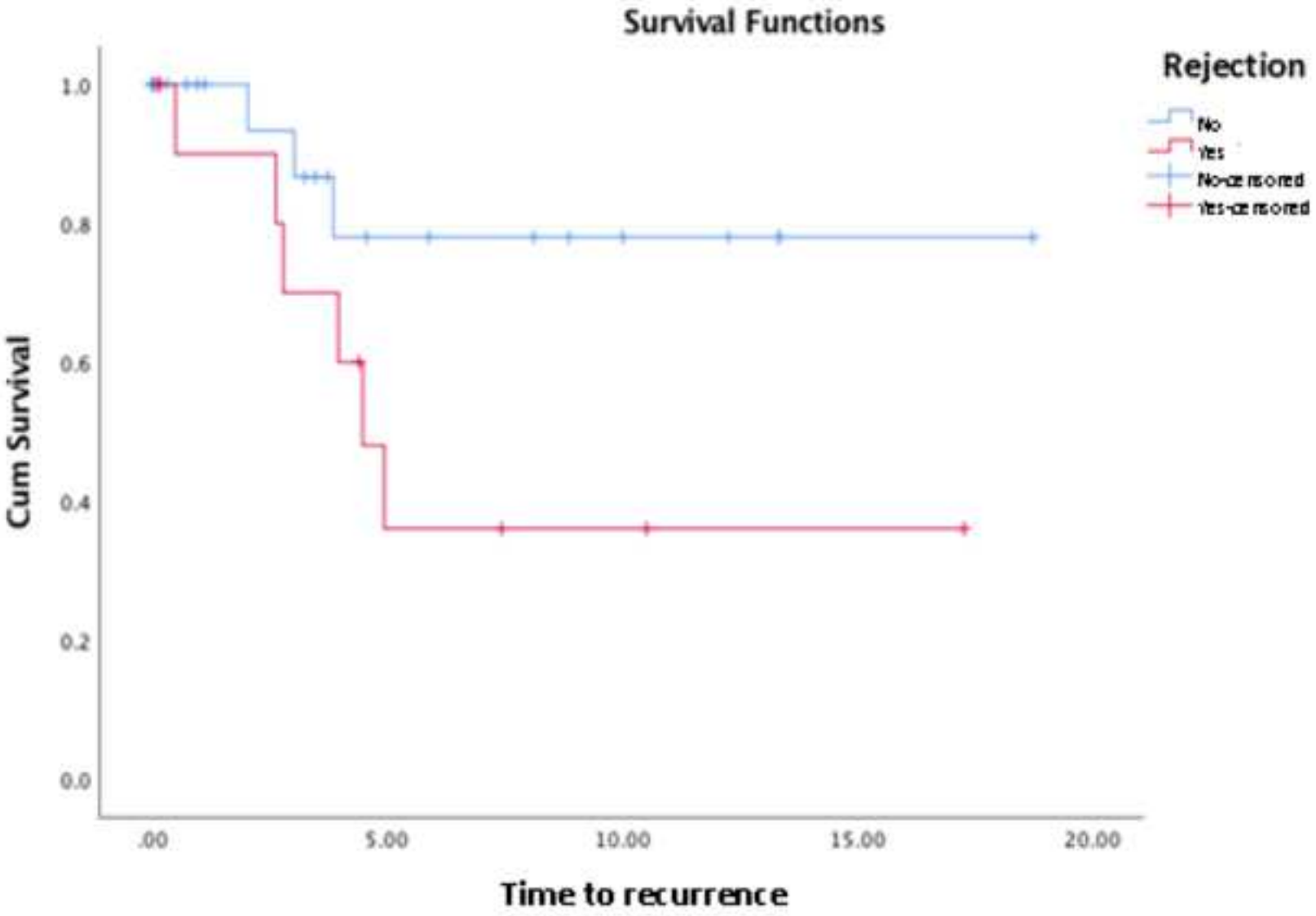

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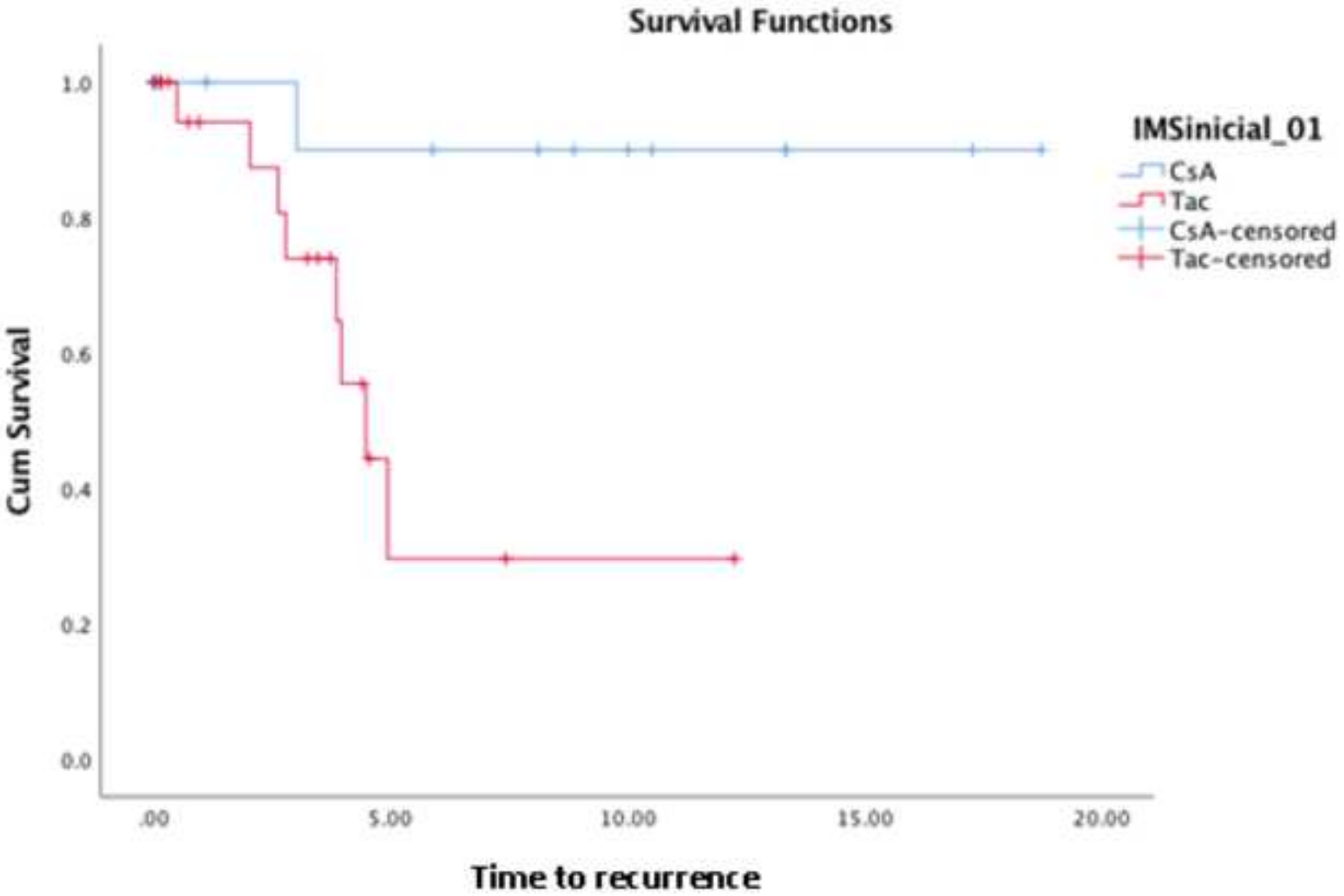

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Title and Abstract

Title	Autoimmune hepatitis – a clinical approach
Abstract	Autoimmune hepatitis is a complex disease with undefined pathophysiology, heterogenous clinical manifestations, several antibodies and different histological findings. It can be classified in type 1, type 2 or overlap syndrome, which leads to different prognosis and treatments. Not only it is a challenge to diagnose, but also to find the best treatment, ranging from medical – immunosuppression – to surgical – transplantation. Recurrent and *de novo* autoimmune

hepatitis after liver transplantation are also two identities still far from being defined. This article aims to review the state of art of autoimmune hepatitis on pathophysiology, etiology, clinical features, treatment and prognosis, while also focusing on clinical approach. By making this article, we hope to present in a practical way the current most important aspects of autoimmune hepatitis, with a structure that allows for a clinical and critical thought.

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Autoimmune hepatitis – a clinical approach

Resumo

A hepatite autoimune é uma doença complexa com fisiopatologia indefinida, manifestações clínicas heterogéneas, vários anticorpos e diferentes achados histológicos. Pode ser classificada em tipo 1, tipo 2 ou síndrome de sobreposição, o que leva a diferentes prognósticos e tratamentos. Não só é um desafio diagnosticar, mas também encontrar o melhor tratamento, podendo variar desde a imunossupressão até ao transplante hepático. Hepatite autoimune recorrente e de novo após o transplante de fígado são também duas identidades ainda longe de serem definidas. Este artigo tem como objetivo rever o estado da arte da hepatite autoimune em termos de fisiopatologia, etiologia, características clínicas, tratamento e prognóstico, enquadrado numa abordagem clínica. Ao elaborar este artigo, esperamos apresentar de forma prática os aspetos mais importantes da hepatite autoimune, com uma estrutura que permita um pensamento clínico e crítico.

Abstract

Autoimmune hepatitis is a complex disease with undefined pathophysiology, heterogenous clinical manifestations, several antibodies and different histological findings. It can be classified in type 1, type 2 or overlap syndrome, which leads to different prognosis and treatments. Not only it is a challenge to diagnose, but also to find the best treatment, ranging from medical – immunosuppression – to surgical – transplantation. Recurrent and *de novo* autoimmune hepatitis after liver transplantation are also two identities still far from being defined. This article aims to review the state of art of autoimmune hepatitis on pathophysiology, etiology, clinical features, treatment and prognosis, while also focusing on clinical approach. By making this article, we hope to present in a practical way the current most important aspects of autoimmune hepatitis, with a structure that allows for a clinical and critical thought.

Introduction

Autoimmune hepatitis (AIH) is a complex disease of anomalous immune response against liver tissue, being the result of interaction between genetics, immune system, and environmental factors[1]. It is characterized by a triad of interface hepatitis with lymphoplasmacytic infiltration, hypergammaglobulinemia and various circulating autoantibodies[2]. Currently, its diagnosis is challenging since requires ruling out other chronic liver diseases that may have resembling clinical features[3]. AIH usually has a good response to immunosuppressive therapy, but in 10-20% of patients there is a progression for cirrhosis and end-stage liver disease requiring liver transplantation[4]. Following liver transplantation, acute allograft rejection and relapse of AIH occurs on a significant percentage of patients[5]. This review discusses the clinical approach of AIH focusing on physiopathology, clinical features and treatment, while also reviewing recent achievements.

Epidemiology

Autoimmune hepatitis has a global distribution with reported cases in all ethnic groups, ages and genders[6-8]. There is a female to male ratio of 3,6 to 1. It's associated to a higher prevalence in north American and northern European white persons with high frequency of HLA-DRB1*03 and HLA-DRB1*04[9]. It is responsible for 4 to 6% of adult liver transplantations in Europe and United States[10].

Etiology and physiopathology

As many autoimmune diseases, currently it is believed that the cause of AIH results from a complex interaction between an environmental trigger, individual's genetic predisposition and the immune system[11]. There is a clear association between the human leukocyte antigens (HLA)-DR3 and HLA-DR4 and AIH[9]. Different triggers have been identified, such as viruses – measles virus, hepatitis A, hepatitis B, hepatitis C and Epstein's-Barr virus[12-17] – drugs – diclofenac, methyldopa, oxyphenisatin, nitrofurantoin and minocycline[18] – and toxins. The precise mechanisms are still unknown.

The strongest immunopathology mechanism hypothesis for AIH is the epitope mimicry, in which there is presentation of an environmental trigger with homologies of the host antigens that leads to bystander activation of resting autoreactive T lymphocytes[19]. This will cause a cross-reaction and, subsequently, a loss of self-tolerance, which provokes an immunopathologic response and, therefore, an immune reaction against the host tissue [19]. The time between exposure and onset of disease can be long, and the presence of the trigger agent is no need for the perpetuation of the disease [20]. The CD4+ or helper T (Th) cell is the main effector cell, being its activation the first step of the pathogenic pathway[21].

Another proposed pathogenic mechanism for AIH is the epitope spreading or exposure of hidden autoantigens due to hepatocellular injury[19]. This will lead to presentation of an autoantigen via MHC and costimulatory molecules which will produce several cytokines, leading to differentiation of uncommitted CD4 T-helper cells (Th0) to Th1-cells (secretion of interferon-γ), Th-17 (secretion of IL-17) or Th2 (secretion of IL-13, IL-4), indicating that all these effector cells could be involved in AIH pathogenesis. This can be explained by a decrease in the immunoregulatory mechanisms. This decrease is not fully understood, but current data point in a malfunction of regulatory T-cells, particularly CD4+CD25+FOXP3+ T-cells[22].

Clinical features

Autoimmune hepatitis has a fluctuate and heterogeneous behaviour. To simplify, clinicians categorize it in 3 major groups. It can present as: i) an acute icteric hepatitis, which can be a challenge to diagnosis, since its clinical and biochemical parameters are compatible with an acute viral hepatitis[23]; ii) an oligosymptomatic mild to moderate chronic disease, with clinical presentation similar to other forms of chronic hepatitis[24]; or iii) asymptomatic and therefore unrecognized disease, which later on will mostly be diagnosed as “cryptogenic” cirrhosis[25, 26]. The most common symptom is ready fatigability (86%) while the most common physical finding is hepatomegaly (78%). Jaundice is found in 69% of patients[25, 26].

As many immune-mediated diseases, AIH is usually presented with other autoimmune disorders. Ranging between 4 to 44%, patients present other

concurrent conditions, being autoimmune thyroiditis, Grave's disease and rheumatoid arthritis the most common[27]. Thyroid disorders and rheumatoid arthritis are usually associated with younger patients, whereas ulcerative colitis or autoimmune haemolysis are more common in older patients[27]. It is important to notice that these conditions may obscure the diagnosis of AIH, so clinicians must be aware of these associations[27]. Plus, it's crucial to mention that AIH is associated with negative effect on health-related quality of life[28].

Laboratory features

The major biochemical markers in AIH are serum aminotransferase activity, with a predominance of aspartate aminotransferase (AST), bilirubin concentrations, serum alkaline phosphatase and hypergammaglobulinemia. Both aminotransferase activity and bilirubin concentration are usually elevated (over 50 times upper normal limits), while serum alkaline phosphatase can be normal or elevated[29]. Nevertheless, aminotransferase and bilirubin levels vary from individual and over time, so are not considered good methods for AIH diagnosis[30]. Specifically in AIH, hypergammaglobulinemia has a disproportional increase of immunoglobulin G (IgG), which may be elevated even if the total concentration of immunoglobulins are normal[29].

Serologic tests are paramount for the diagnosis of AIH, and should always be done when there is clinical, laboratory and/or histological suspicion. The three major autoantibodies in this disease are antinuclear antibodies (ANA), smooth muscle antibodies (SMA) and liver kidney microsomal type 1 antibody (anti-LKM1)[31]. If negative and clinical suspicion remains, anti-soluble liver antigen/liver-pancreas antibodies (anti-SLA/LP) may be useful to search [32]. Both ANA and SMA are not disease nor organ specific, but its detection together constitutes a good serologic exam, with high sensibility and specificity[33]. Anti-LKM is positive usually when both ANA and SMA are negative, being strongly associated with paediatric patients. Anti-SLA/LP has a very high specificity for AIH (99%) but are not present in most patients. It has been proven to have prognostic value[34].

Other serologic markers of AIH are atypical pANCA[32], anti-actin[35], anti-asialoglycoprotein receptor[36] and anti-liver cytosol type 1[37].

Histology

Contrary to some autoimmune diseases, there is no pathognomonic histological features in AIH. The most common histological feature in AIH is interface (para-septal or periportal) hepatitis with a lymphoplasmacytic necro-inflammatory infiltrate[38]. Other histological findings are infiltration of plasma cells, rosettes, necrosis of pyknotic (apoptotic) cells, ballooning degeneration of hepatocytes (39%) and emperipolesis (penetration of one cell into and through a larger cell)[38, 39]. Presence of fibrosis alongside these findings is typical in AIH. Development to advanced fibrosis and cirrhosis may occur rapidly in AIH[23, 24]. Acute severe (fulminant) has a proposed histologic diagnosis – lymphoplasmacytic infiltration around the central vein with hepatocyte drop-out or necrosis, which is usually associated with lymphoid aggregates and plasma cell infiltration[40].

Diagnosis

Clinical criteria

Due to the absence of pathognomonic features in AIH, diagnosis of this disease requires the combination of symptoms and physical exam, laboratory findings, serology and histology[30] (table I). It is necessary to exclude other hepatic diseases such as viral hepatitis, alcoholic hepatitis, drug-induced hepatitis, hemochromatosis, Wilson disease, α1-antitrypsin deficiency, primary biliary cirrhosis, and primary sclerosing cholangitis[30]. Laboratory findings should include abnormal elevation of serum gamma globulin and/or IgG levels[30]. Serology compatible with AIH includes positive antinuclear antibodies (ANA), smooth muscle antibodies (SMA) or antibodies to liver-kidney microsome type 1 (LKM1)[30], which helps classify between type 1 or type 2 AIH. On the histologic examination, interface hepatitis should be present, which may be associated with plasma cell infiltration, hepatocyte rosettes and/or centrilobular necrosis[30]. According to the presence of etiologic factors or the degree of immune reactivity, it can be differentiate between definite or probable AIH[30].

Table I - Diagnostic algorithm for autoimmune hepatitis [30]

Presenting features	Acute, chronic or acute severe onset Serum AST-to-alkaline phosphatase ratio > 3

	Elevated serum gamma globulins, IgG and/or AST	
Necessary exclusions	AMA - Normal cholangiogram if UC or cholestasis Ceruloplasmin normal Normal α1-antritrypsin phenotype Transferrin saturation inferior to 45% Non-alcoholic or drug-induced hepatitis HAV, HBV and HCV markers negative	
Histological findings	Interface hepatitis with or without plasma cell infiltration, hepatocyte rosettes and/or centrilobular necrosis	
Diagnosis	**Definite AIH** Gamma globulins and/or IgG superior to 1,5 ULN ANA, SMA or anti-LKM1 superior or equal to 1:80 No drugs or blood products Alcohol intake inferior to 25g/day	**Probable AIH** Gamma globulins and/or IgG inferior to 1,5 ULN ANA, SMA or anti-LKM1 inferior or equal to 1:40 Previous drugs or blood products Alcohol intake inferior to 50g/day Nonstandard liver-related autoantibodies present
Type	**Type 1 AIH** **SMA and/or ANA +**	**Type 2 AIH** **Anti-LKM1 +**

Scoring criteria

The purpose of scoring systems is for research and should not be used as a discriminative diagnostic index, but rather to ensure a uniform evaluation of each single patient. The original scoring system (table II) was developed during 1992 with an update at 1999[30]. A simplified score (table III) was developed during 2008, and uses only 5 categories: autoantibodies, viral disease, immunoglobulin level, histologic findings and pre-treatment aggregate score[41]. Both scores have already been compared, having the simplified score a better specificity (90 vs 73%) and predictability (92 vs 82%), while the original scoring system has better sensitivity (100 vs 95%)[41].

Table II – Revised original scoring system for the diagnosis of autoimmune hepatitis - Adapted from [30].

Category	Variable	Score
Gender	Female	+2
Alk Phos: AST (or ALT) ratio	>3	-2
	<1,5	+2
Gamma globulin or IgG level	>2,0 times ULN	+3
	1,5-2,0 times ULN	+2

	1,0-1,5 times ULN	+1
	<1,0 times ULN	0
ANA, SMA or anti-LKM1 titres	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
AMA	Positive	-4
Viral markers of active infection	Positive	-3
	Negative	+3
Drug history	Yes	-4
	No	+1
Alcohol	<25 g/day	+2
	>60 g/day	-2
HLA	DR3 or DR4	+1
Concurrent immune disease	Thyroiditis, UC, synovitis, others	+2
Other autoantibodies	Anti-SLA, actin, LC1, pANCA	+2
Histologic features	Interface hepatitis	+3
	Plasmacytic infiltrate	+1
	Rosettes	+1
	None of the above	-5
	Biliary changes	-3
	Other features	-3
Treatment response	Complete	+2
	Relapse	+3
Pre-treatment score		
Definite diagnosis		>15
Probable diagnosis		10-15
Post-treatment score		
Definite diagnosis		>17
Probable diagnosis		12-17

Table III – Simplified scoring system for the diagnosis of autoimmune hepatitis, adapted from[41].

Category	**Variable**	**Score**
Autoantibodies		
ANA or SMA	1:40	+1
Anti-LKM1	≥1:80	+2
	≥1:40	+2
Anti-SLA	Positive	+2
Immunoglobulin level		
IgG (times above upper limit of normal)	>1	+1
	>1,1	+2
Histologic findings		
	Compatible	+1

Morphologic features (relation to autoimmune hepatitis)	Typical	+2
Viral disease		
Absence of viral hepatitis	No viral markers	+2
Pre-treatment of viral hepatitis		
Definite diagnosis		≥7
Probable diagnosis		6

Classification and variants

Type 1 autoimmune hepatitis

Type 1 AIH is characterized by a specific serology and a different behaviour from other variants. It is associated with the detection of antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA). Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) can be present up to 90% in type 1 AIH, contrary to type 2, in which is rarely present. It occurs at any age or gender and has a female-to-male ratio of 3,5:1. Extrahepatic autoimmune diseases are commonly associated such as autoimmune thyroiditis or type 1 diabetes[42]. It usually presents an abrupt onset of symptoms, but it can present itself in fulminant form[43].

Type 2 autoimmune hepatitis

Type 2 AIH is strongly associated with antibodies against liver kidney microsome type-1 (LKM1) [44]. Contrary to type 1, most patients are children (2 to 14 years), even though it can appear on adults. Concurrent autoimmune diseases are present in many cases, having already been associated with type 1 diabetes *mellitus*[45]and vitiligo[46], for example. Acute and fulminant onset are possible presentations[47].

Nonclassical presentations

Asymptomatic patients

AIH can have an asymptomatic presentation in 34-45% of cases, with compatible histological characteristics of AIH [25, 26]. This group can have histological improvement without any medical intervention, but it's rare and most of the cases incomplete[48]. Progression to cirrhosis and liver failure are possible[48].

Due to its aggressive inflammatory activity, it justifies treatment, independently of symptoms or severity. This is stated by comparing untreated patients with mild asymptomatic AIH and treated patients with severe symptomatic AIH. The 10-year survival is superior in the treated group (67 vs 98%)[49].

Acute severe (fulminant) presentation

While constituting only 6% of cases, being aware of this variant is important due to its severity [40]. This presentation represents one of the most arduous diagnosis, for different reasons. It can have a clinical behaviour similar to an acute viral or toxic hepatitis [47], with marked serum aminotransferase elevations and histologic changes such as massive hepatic necrosis, plasma cell infiltration, centrilobular necrosis and lymphoid follicles. Unlike other types, typical histologic and laboratory findings are usually absent. IgG serum is normal in 25-39% of cases, with ANA absent or weakly positive.

Autoantibody-negative autoimmune hepatitis

This variant is classified when patients with negative ANA, SMA and anti-LKM1 antibodies fulfil the international criteria of the diagnosis of AIH[50]. Representing 13% of cases[51], they have epidemiological, clinical, laboratory and histological features similar with classic AIH, and HLA frequencies compatible to AIH as well. It's important in these cases to exclude other diseases that can mimic AIH behaviour (Wilson disease, celiac-related liver diseases and drug-induced liver disease)[50]. 15-20% of the cases can be reclassified when evaluated for atypical pANCA and anti-SLA antibodies[50].

Drug-induced autoimmune-like hepatitis

Representing 9% of patients diagnosed with AIH, there are several drugs associated with this variant – minocycline and nitrofurantoin (most common – 90% of cases), methyldopa, di-hydralazine, halothane, tienilic acid and oxiphenistatin [52]. This variant usually presents with an acute onset, with jaundice (69%) and hypersensitivity features (fever, rash and eosinophilia – 15-20%)[52]. Histologic findings include classic AIH features and eosinophils. Biopsy can find features than can favour drug-induced injury – portal neutrophils and cholestasis – or favour AIH – portal and intra-acinar plasma cells, hepatocyte rosettes and emperipolesis [39].

Overlap syndromes

Overlap syndromes are define by having a predominant phenotype of AIH, with secondary features of cholestatic liver disease (for this classification, AIH must be the principal phenotype)[53]. Findings of cholestatic diseases are separated in three different groups: primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and cholestatic syndrome with indistinguishable form (AMA-negative PBS or small-duct PSC)[53].

Treatment

Standard treatment

The AIH treatment has two main objectives: induce and maintain remission of the disease activity at a clinical, laboratory and histological level[10]. Currently, the goal of the treatment is a complete normalization of transaminases, bilirubin and IgG levels [10].

Being diagnosed with AIH implies, in most of the cases, the necessity of treatment with immunosuppressive drugs. Nevertheless, it is important to note that some patients may only require monitoring. This clinical option can be weighted if the patient has a low-grade histologic activity, absence of higher fibrosis stages, and enough liver function. Unfortunately, only a minority of patients fulfil these circumstances, and this option is always based on individual circumstances and the preferences of the patient[54].

The standard treatment is based on two pharmacological steps. First, we induce remission with a steroid-based treatment. Second, we maintain that remission with a thiopurine-based treatment. For induction of remission, the most used option is prednisolone between 0,5 to 1 mg/kg/day, and constantly wean over time. For maintenance of remission, the first option is azathioprine 1-1,5 mg/kg/day, in monotherapy or combined with prednisolone, in low-dose[55]. Current European (EASL) guidelines advice to introduce azathioprine 2 weeks after starting steroids, to help differentiate between azathioprine-induced hepatotoxicity and primary non-response, when faced with persistent pathological levels of liver enzymes[56].

As an alternative to prednisolone to induce remission, European Association for the Study of Liver (EASL) proposes budesonide with a starting dose of 9 mg/day, which has proved better results in both remission and less side effects. However, according to a recent survey, this option was not used by a

single expert hepatologist, due to the greater and successful experience with other treatments[57]. It is also important to mention that, due to being a drug that requires hepatic first pass effect, it is contraindicated in patients with cirrhosis[58].

The duration of immunosuppression is far from being defined, but current studies show patients with AIH demanding a life-long treatment, being the duration of 24 months the minimum required for a stable biochemical remission[56]. In addition, 80% of patients relapse after a 3-year period of discontinuation[59]. Unluckily, a life-long treatment with immunosuppressive drugs is the main responsible for the mortality of AIH, so the possibility of therapy withdrawal should be weighted[56]. Due to a poor correlation between biochemical and histological activity, many centres propose the use of a follow-up biopsy before the discontinuation of the treatment[56].

Alternative and second line treatments

Patients intolerant to standard treatment

A significant minority of patients (10-20%) do not respond to standard treatment. In this group of patients there are two main drugs we can choose. If the patient has normal levels of thiopuridine methyl-transferase (TMPT), thiopurine 6-mercaptopurine (6MP) is a good alternative in patients with intolerance to azathioprine (a prodrug of 6MP)[60]. The thiopurine metabolism creates two final metabolites: 6-methyl mercaptopurine – associated with hepatotoxicity – and 5-thioguanine (6TG) – mediates the therapeutic immunosuppressive effect as well as side effects like myelosuppression. Close monitoring to detect bone marrow toxicity is crucial. In patients with insufficient levels of thiopuridine methyltransferase, mycophenolate mofetil is an option[61].

Patients with insufficient response to standard treatment

When faced with insufficient response to immunosuppressive treatment, the most logical approach should be to increase the dosage of drugs. Nevertheless, this should be balanced with the patient own risk, considering the side effects, infectious complications and the high-risk of progression to cirrhosis in this group of patients.

Calcineurin inhibitors are commonly used in these situations. Both cyclosporine and tacrolimus have improved immunological and biochemical

parameters [10]. A recent study showed MMF had a better response (56,5%) than tacrolimus (34%) in this group of patients[62].

Patients with acute and severe presentation

Current knowledge of AIH treatment is not enough to have a defined algorithm for severe manifestations, with controversy in the use of corticosteroids. Currently, it has been agreed that high dose of steroid treatment can be beneficial in most cases. The optimal dose, response criteria and the best timing for liver transplantation, still, remain undefined. When there is no response to the treatment, patients with severe AIH should be evaluated for liver transplantation[63].

Patients with paediatric-onset disease

AIH in adults and in children have different presentations. In children, autoimmune sclerosing cholangitis (ASC) – overlap syndrome and primary sclerosing cholangitis - is present up to 50% of patients with AIH. This justifies the alteration of the therapeutic regimen. The treatment algorithm is similar to classic AIH, with addiction of ursodeoxycholic acid at a daily dose of 15-20 mg/day[64]. It is important to mention that paediatric-onset disease has a higher percentage of liver transplantation, recurrent flares and death[65].

Prognosis

Different clinical aspects can predict the prognosis of AIH patients. A score of 12 or more points at presentation by MELD score identifies 97% of patients that will fail conventional glucocorticoid therapy and will require liver transplantation or die of liver failure[42]. Positivity of anti-SLA at presentation unquestionably defines that those patients will relapse after glucocorticoid withdraw[66]. Response to initial medical treatment also helps to predict worse prognosis. Patients who, after 12 months of standard treatment, fail to achieve normal or near normal levels at laboratory tests or liver histology have higher frequency of liver transplantation (15 vs 2%) and progression to cirrhosis (54 vs 18%)[67]. Curiously, young adults have a higher frequency of treatment failure than older people (20 vs 7%)[68].

AIH and tumour surveillance

A recent meta-analysis proved there is an incidence rate of hepatocellular carcinoma in AIH patients of 3,06 per 1000 patients by year, being almost all cases associated with cirrhosis. Furthermore, the incidence rises to 10,07 per 1000 patients by year in whom already have cirrhosis, being lower than cirrhosis associated with viral hepatitis[69]. However, AIH-cirrhosis cases might benefit from hepatocellular carcinoma surveillance. Abdominal US every 6 months should be considered. Due to the duration of immunosuppressive therapy, 5% of patients with AIH have extrahepatic malignancies.

Liver transplantation

Liver transplantation is the current main surgical treatment for AIH, representing 4% of all liver transplantations done in Europe and North America[10]. It should be considered in AIH patients who either develop end-stage liver disease despite treatment or develop fulminant hepatic failure (with encephalopathy) without corticoid response. It's associated with a 5 and 10-years survival of 83 and 75% respectively with graft survival of 92%. Relapse happens on 20-36% of patients[19, 70]. De novo AIH occurs in 6-10% of patients[71].

After liver transplantation, immunosuppression is required. Most common pharmacological regime used in these situations is calcineurin inhibitor together with AZA or mycophenolate and corticosteroids, though there is still no optimal regimen established[72].

After LT, patients grafted for AIH are at a higher risk for acute and chronic rejection. Due to this, reduction of immunosuppressive regimen should be performed cautiously. Two risk factors have been identified for chronic rejection: young age of transplantation and moderate to severe acute rejection[73].

Recurrent autoimmune hepatitis

Recurrence of primary disease after liver transplantation has become a prime issue for both clinicals and researchers. Recurrence is defined by the reappearance of the primary disease in the allograft. Due to longer survival and increasing success of liver transplantation, the recurrence of the primary disease has become a fundamental aspect of morbidity and mortality post transplantation. Criteria for diagnosis of recurrent AIH is still not established, though the hallmark is interface hepatitis with or without plasma cells that can include other aspects

such as acute lobular hepatitis with focal hepatocyte necrosis, pseudo-rosetting of hepatocytes or acidophil bodies with lymphoplasmacytic cells[74]. Current evidence shows that the role of autoantibodies for diagnosing recurrent AIH are still uncertain[5]. Risk factors for recurrent AIH following LT are not fully understood. Treatment of recurrent AIH is usually empiric, based on restarting or intensifying corticosteroid therapy, add new immunosuppressive drugs or reinforce adherence to medical therapy[75].

De novo autoimmune hepatitis

De novo autoimmune hepatitis is characterized by a clinical syndrome mimicking AIH in patients transplanted for nonautoimmune liver disease[71]. These patients undergo liver transplantation and feature afterwards high levels of IgG, serum autoantibodies and histological findings compatible to classic AIH[71]. The standard treatment for *de novo* autoimmune hepatitis are based on corticosteroids.

Conclusion

AIH is a complex disease with ongoing challenges both on diagnosis, medical treatment and transplantation. Further studies are required to determine optimal management.

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