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*MINIREVIEWS*

# Autoimmune hepatitis in genetic syndromes: A literature review

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## Abstract

Genetic syndromes represent relevant and rare diseases. These conditions include a large amount of epidemiological, pathogenetic and clinical features. However, a systematic approach to genetic syndromes is often prevented by the rareness of these diseases. So, although clinical features are usually precisely defined, nowadays more uncommon associations between genetic syndromes and internal medicine related diseases have been insufficiently studied. Autoimmune hepatitis (AIH) is a chronic liver disease caused by loss of tolerance to hepatocyte-specific auto-antigens. Conversely, a better knowledge about specific genetic syndromes in which AIH is more frequent could be important in the clinical management of patients, both for an early diagnosis and for a prompt therapy. Furthermore, a systematic approach could explain if onset, clinical course, and response to treatment of AIH are typical for specific genetic syndromes. We took in consideration all the scientific articles reported in PubMed in the last 10 years, from 2010 to 2020. The purpose of this review is to explore the prevalence of AIH in genetic syndrome, but also to suggest new classification, that could be useful for pathogenetic hypothesis and clinical approach to genetic syndrome. From the 139 publications selected using keywords "autoimmune hepatitis" and "genetic syndrome", 30 papers (21.6%) respected the chosen inclusion criteria, reporting the association between AIH in patients with a genetic syndrome. We have collected in all 47 patients with AIH and genetic syndrome, and with median age of 12.6-year-old. We suggest that when a patient presents a clinical picture of cryptogenic chronic hepatitis, that is unexplained, it is useful to explore differential diagnosis of AIH associated with genetic syndrome. Given the clinical relevance of this topic, further reports are needed to demonstrate our hypothesis and collect new evidence in this field.

**Key Words:** Autoimmunity; Hepatitis; Gene; Syndrome; Liver; Disease; Immunity

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**Core Tip:** Autoimmunity is a relevant health problem, burdened by delay in diagnosis and difficult therapeutic approach. Genetic syndromes often include autoimmune diseases in their typically complex clinical picture. This review explores the association between genetic syndromes and a specific autoimmune disease, autoimmune hepatitis in order to understand if there are pathogenetic mechanisms based on specific mutations, but also how much autoimmune hepatitis is frequent in genetic syndromes. This systematic approach showed an interesting correlation between these two important groups of diseases.

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## INTRODUCTION

Rare genetic diseases are a topic of relevant importance for multi-organ complications and complex clinical pictures. These conditions include a large amount of epidemiological, pathogenetic and clinical features. The most of them have defined DNA mutations, typical phenotypes and characteristic clinical courses. Auto-inflammatory and autoimmune complications are described in several genetic syndromes. This occurs more often when immunoregulatory genes are involved in the pathogenesis of the disease.

The autoimmune hepatitis (AIH) is a complex immune-mediated and chronic liver disease, caused by loss of tolerance to hepatocyte-specific autoantigens.

It is an autoimmune disease of unknown etiology. There is no clear evidence for a hereditary etiology of this disease. Association studies of major histocompatibility complex and other genes demonstrate an influence of immunogenetics[1].

The AIH have annual incidence ranges from 0.67 cases to 2.0 cases per 100000 and annual prevalence ranges from 4.0 to 24.5 per 100000 people depending on the geographical location[2]. Familial cases of AIH are reported to occur in only 1% of AIH cases[3]. This observation suggests role of genetic predisposition. The pathophysiologic mechanisms of AIH are not fully understood. Both genetic predisposition and an imbalance between effector and regulatory immunity are key pathologic factors for disease development[1,2]. Due to an aggressive course of the disease, the diagnosis must be made early and therapy with steroids and immunosuppressant drugs started [1,4].

In 2015, we described a 6-year-old girl with Noonan syndrome (NS) and AIH type 1 [5]. Molecular analysis of *PTPN11* gene showed heterozygous mutation c.923A>G (Asn308Ser) in exon 8. This was the second case described in literature of association between NS and AIH type 1. We supposed that it was not a causality and we thought that autoimmunity represents a characteristic of NS, even if the etiopathogenesis is still unknown.

Then in 2018, we published with Le Coz *et al*[6] two cases with *ctla-4* haploinsufficiency, due to heterozygous microdeletions of chromosome 2q, complicated by autoimmune manifestations. One of these patients had AIH. It is known that about 15% to 20% of patients with the autoimmune polyglandular syndrome type 1 (APS1), also referred to as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), a rare disease with prevalence of 1-9:1000000, suffer from an autoantibody-positive AIH, linked to mutations in the autoimmune regulator gene (AIRE)[1,7].

In this review we report literature data of association between AIH and genetic syndromes. Through a detailed and systematic analysis of the literature, we aim to evaluate AIH as a possible complication in patients affected by a genetic syndrome.

We do a systematic review through the choice of the best current works and which refer to the association between AIH and patients with genetic syndrome diagnosis.

The purpose of this work is to evaluate how many reports of genetic syndromes have AIH as a complication and to suppose pathogenetic mechanisms related to the causative mutation of the syndrome and the autoimmune or autoinflammatory processes that may have the liver as a target organ. The correlation between AIH and

genetic syndromes is still controversial and the cause and effect relationship is under investigation in order to understand if it is a simple coincidence/co-occurrence.

When a genetic syndrome has the possibility of developing AIH, the monitoring of this risk is a non-negligible aspect during the follow-up of these patients. AIH is a severe complication, which can have an unfavorable outcome, even with the death of the patient. Indeed, the untreated AIH has a very poor prognosis, with reported survival rates of 50% and 10% at 5 and 10-years respectively[4]. We also investigate the etiopathogenetic hypotheses related to the underlying genetic conditions. Besides, as more is becoming understood, it is also clear that in some cases, there is important overlap between genetic disease causation and the development of AIH.

Any classification is arbitrary and should be considered as a new proposal, as an evolving classification. Here, we try to distinguish the influence of genetic factors in causing AIH complication in a specific population, like patients with a genetic syndrome. We present the state of the art, by reporting all the well described cases, reported in literature.

The collection of clinical evidence could increase the knowledge in this field, improving the management of rare syndromes and AIH, as possible complication with high morbidity and mortality.

## METHODOLOGY

We conducted a standard systematic literature review on PubMed, using the combination of keywords: "autoimmune hepatitis", "liver disease", "genetic syndrome".

The application of these search terms aimed to cover most of the publication regarding the description of the association of AIH and genetic syndromes.

We consider only those studies in which the above-mentioned terms are present, alone or variously combined together, in the main text, in the title, in the abstract and in MeSH terms. Since genetic syndromes are rare diseases, we have chosen both previous reviews and case reports. We took in consideration all the scientific articles reported in PubMed in the last 10 years, from 2010 to 2020. The search performed on February 17$^{th}$, 2021 retrieved 8094, if we use combination of "liver disease" and "genetic syndrome" as keywords, while there are 139, if the combination used is "autoimmune hepatitis" and "genetic syndrome". The inclusion criteria include a clear clinical diagnosis of AIH and genetic syndrome. We checked in each article the congruence of the diagnosis of AIH with the recognized criteria and the confirmation of the diagnosis of specific genetic syndrome with a proper genetic test. Of 139 articles, 30 are accessible, compatible with our inclusion criteria and are included in the analysis. The exclusion criteria for the remaining 109 articles are in a language different from English, regarding familiar but not syndromic cases and a not specific diagnosis of AIH.

It has been paid attention to diagnostic criteria in diagnosis of AIH[1]. According to the Ab profile, AIH can be divided into three subtypes: AIH type 1 by the presence of antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA); AIH type 2 by anti-liver-kidney microsomal autoantibodies (LKM-1) directed against cytochrome P450 (CYP) 2D6; AIH type 3 by autoantibodies against a soluble liver antigen (SLA/LP)[1,2].

The established specific diagnostic criteria and scoring systems of AIH include analysis of autoantibodies (ANA, SMA, anti-LKM1, and anti SLA), immunoglobulin (Ig) G, viral markers (IgM anti-HAV, HBsAg, HBV DNA, and HCV RNA) and histological findings[1,2,8]. The diagnosis of syndromes condition is confirmed through genetic tests, using a cytogenetic, cytogenomic or molecular approach.

## RESULTS

From the 139 publications selected using keywords "autoimmune hepatitis" and "genetic syndrome", 30 papers (21.6%) respected the chosen inclusion criteria, reporting the association between AIH in patients with a genetic syndrome.

From 2010 to 2020, the articles which have reported AIH as complication of a genetic syndrome have a median of 1.7% of all scientific production on liver disease in genetic syndromes, with a peak between 2014 and 2015 years of publication.

There are many case reports (24/30) and some reviews (2/30) and few original or research articles, cohort studies or clinical trials. Here, we considered the review which described case reports, because of the rarity of diseases.

Most of the syndromes found are forms of immunodeficiency or immunodysregulation, such as APS1, Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome (IPEX), Immunodeficiency-centromeric instability-facial anomalies syndrome, spondilocondrodisplasia (SPENCDI), X-linked agammaglobulinemia (XLA), Shwachman-Diamond syndrome (SDS) and severe combined immunodeficiency (SCID).

A new findings are the unbalanced genomic diseases, like Down syndrome, Smith-Magenis syndrome (SMS), 22q13.3 deletion syndrome and 2q deletion syndrome.

Interesting is the presence of 2 articles about Wilson disease (WD), that is a disease with primary hepatic involvement, describing 2 patients in which a form of autoimmune liver disease is hypothesized.

Moreover, we found some very different syndromes in association with AIH: NS, cutaneous amyloidosis, H syndrome, familial hemophagocytic lymphohistiocytosis (FHL) with STXBP2 mutations, progressive familiar intrahepatic cholestasis type 3 (PFIC3) and sclerosis tuberous syndrome (TSC).

We have collected in all 47 patients, with variable age of AIH onset. We observed median age of patients of 12.6-year-old and a high incidence (70.2%) of patients with age < 12-year-old. The ratio of males to females is 40.4% to 55.3% respectively, with female prevalence. The 30% of patients were died. We found also some publication that includes pathogenetic hypothesis, which are reported and commented in the discussion.

The articles and case reports are described in Tables 1-3.

## DISCUSSION

AIH is a relatively rare progressive chronic liver disease that mainly affects women and is usually characterized by increased IgG levels, circulating autoantibodies and a favorable response to immunosuppressive treatment[1,2,4]. The etiology of AIH is still unknown and all the causes of chronic liver disease must be excluded in advance before diagnosing AIH. The literature data exhibit that AIH can show up in any age of both sexes and all ethnic groups, with peaks around puberty and between 4$^{th}$ and 6$^{th}$ decades. The onset of AIH may be insidious, acute or chronic, and one third of patients have already developed cirrhosis at the moment of diagnosis, suggesting a delay in diagnosis[8]. The presence of other autoimmune or immune-mediated diseases is frequent and an unusual form of AIH has been reported in 10%-18% of patients with APECED, also known as APS1[7-9]. AIH develops in genetically predisposed individuals, after exposure to triggering factors like microbes, viruses or drugs. When the autoimmune attack against the liver starts, it continues through "molecular mimicry" mechanisms, and is promoted by the diminished control of regulatory T-cells[8].

The evidence of an hepatic CD4 and CD8 T cell and B cell infiltration confirms the immune-mediated pathogenesis, related to defective regulatory mechanisms, antigen-specific immunization, pro-inflammatory CD4 T cell and their cytokines profile. The dysregulation of adaptive immune response has a pathogenetic role, due to the production of autoantibodies and the persistence in the liver of autoreactive CD4 T cells that maintain inflammation with a predominant secretion of tumor necrosis factor (TNF), interferon-γ (IFN-γ), interleukin (IL)-21. Furthermore, T-reg cell are not able to stop inflammation[10].

AIH is principally divided in type 1 (AIH-1) and type 2 (AIH-2), based on autoantibodies. The authors confirm that there are many differences between two types. AIH-2 is more frequent in children and young adults, has an acute or severe course and treatment failure, with relapse after stopping treatment and need for long-term treatment, compared to AIH-1[8,11,12]. A panel of experts, namely International AIH Group (IAIHG), reported the descriptive criteria of AIH, updated periodically [13]. Some AIH patients has clinical cholestatic presentation, that is known as primary biliary cholangitis or primary sclerosing cholangitis (PSC). In 2001, Gregorio *et al*[14] introduced the term "autoimmune sclerosing cholangitis" for the patients characterized by lesions of both AIH and sclerosing cholangitis. This presentation was named "overlap syndromes or variants of AIH" and its appearance was more frequent in children. The authors suggested an investigation of the biliary tree in all children with a diagnosis of AIH[8,15]. The IAIHG do not support the concept of "overlap

**Table 1 Group-1: Disease gene is one of immunoregulatory genes**

| Genetic syndrome | Inheritance | Gene | Ref. | Number of AIH cases | Sex | Age at diagnosis | Nucleotide variant | Protein variant | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| APECED/APS1 | AD, AR | *AIRE* | Meloni *et al* [17], 2017 | 6 | F; F; F; F; M | 3 yr; 6 yr; 11 yr; 5 yr; 8 yr; 12 yr | c.[415C>T];[415C>T] | p.[(R139X)];[(R139X)] | Alive; Alive; Death; Death; Alive; Alive |
| | | | Huibregtse *et al*[7], 2014 | 1 | F | 10 yr | c.[20_115de196];[967_979del13] | p.[(?)];[(?)] | Alive |
| | | | Zaidi *et al* [18], 2017 | 2 | M; M | 3 yr; 5 yr | NR | NR | Alive; Death |
| IPEX | XLR | *FOXP3* | López *et al* [21], 2011 | 1 | M | 4 yr | c.[748-750delAAG];[0] | p.[(250Kdel)];[(0)] | Alive |
| | | | Baris *et al* [22], 2014 | 1 | M | 3 yr | c.[816+5G>A];[0] | p.[(?)];[(0)] | Death |
| | | | Magg *et al* [23], 2018 | 1 | M | 3 yr | c.[816+2T>A];[0] | p.[(?)];[(0)] | Death |
| | | | Duclaux-Loras *et al* [20], 2018 | 3 | M; M; M | 4 wk; 4 wk; 3 wk | c.[751_753delGAG]];[0]; c.[1157G>A];[0]; c.[227delT];[0] | p.[(E251del)];[(0)]; p.[(R386H)];[0]; p.[(L76Qfs*53)];[(0)] | Death; Death; Alive |
| ICF2 | AR | *ZBTB24* | von Bernuth *et al*[25], 2014 | 1 | F | 3 yr | c.[1222T>G];[1222T>G] | p.[(C408G)];[(C408G)] | Alive (not responding to therapy) |
| ICF1 | AR | *DNMT3B* | Sterlin *et al* [24], 2016 | 1 | M | 5 yr | c.[2324C>T];[2324C>T] | NR | Alive |
| SPENCDI | AR | *APC5* | Briggs *et al* [26], 2016 | 3 | F; F; F | 9 yr; 3 yr; 6 mo | c.[725A>G];[725A>G]; c.[389+1G>A];[389+1G>A]; c.[131C>T];[712T>C] | p.[(H242R)];[(H242R)]; p.[(?)];[(?)]; p.[(T44M)];[(C238R)] | Alive; Alive; Alive |
| SDS | AR | *SBDS* | Veropalumbo *et al*[28], 2015 | 2 | NR; NR | 9 mo; 12 mo | c.[258+2T];[183-1847A>CT]; c.[258+2T>C];[183-184TA>CT] | p.[(?)];[(?)]; p.[(?)];[(?)] | Alive; Alive |
| SCID | AR | *CD3γ* | Tokgoz *et al* [30], 2013 | 1 | F | 12 yr | c.[IVS2-1G>C];[IVS2-1G>C] | p.[(?)];[(?)] | Alive |

AIH: Autoimmune hepatitis; AD: Autosomal dominant; AR: Autosomal recessive; XLR: X-linked recessive; F: Female; M: Male; NR: Not reported; SDS: Shwachman-Diamond syndrome; SCID: Severe combined immunodeficiency; SPENCDI: Spondilocondrodisplasia; ICF: Immunodeficiency, centromeric instability and facial dysmorphism; IPEX: Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome; APECED: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APS1: Autoimmune polyglandular syndrome type 1.

syndromes" as new and distinct disorders[13].

We suspect that genetic syndromes with particular imbalance of immune response, could represent a genetic predisposition to develop autoimmune disease, especially AIH. Some genetic syndromes are known to have autoimmune complications, for examples APS, IPEX syndrome and Down syndrome. Also in rare genomic imbalance diseases could appear autoimmune complications.

We have found some case reports of patients with genetic syndrome complicated by AIH. The main found syndromes are APS/APECED, IPEX syndrome, unbalanced genomic syndromes, RASopathies.

We propose a classification system for genetic syndromes associated with AIH due to genetics and etiopathogenesis aspects. There are three possible groups: group-1, that includes genetic syndromes whose disease gene is one of immunoregulatory genes, directly involved in AIH pathogenesis; group-2, that includes those syndromes in which there is a polygenic involvement of immune-mediated risk and of AIH pathogenesis; group-3, that includes those in which there is a possible association related to the disease causative mutation, seems to be not directly involved in AIH pathogenesis. For the last group, we try to propose some possible pathogenesis mechanism in AIH development.

**Table 2 Group-2: Polygenic involvement of immune-mediated risk (unbalanced genomic disease)**

| Genetic syndrome | Inheritance | Chromosomal region | Ref. | Number of AIH cases | Sex | Age at diagnosis | Deletion breakpoints [build GRCh37/hg19] | Outcome |
|---|---|---|---|---|---|---|---|---|
| Down syndrome | IC | - | Ravel *et al* [32], 2020 | 1 | M | 29 yr | - | Death |
| SMS | AD, IC | del17p11.2 | Yang *et al* [36], 2014 | 1 | F | 24 yr | chr17: 16,660,721-20,417,975 *dn* | Alive |
| PHMDS | AD | del22q13.31-qter | Bartsch *et al* [37], 2010 | 1 | F | 3 yr | - | Alive |
| del2q | IC | del2q33.1-q34 | Le Coz *et al* [6], 2018 | 1 | F | 12 yr | chr2:197,942,576–209,522,220 *dn* | Alive |

AIH: Autoimmune hepatitis; IC: Isolated cases; AD: Autosomal dominant; F: Female; M: Male; SMS: Smith-Magenis syndrome.

### *Group-1 genetic syndromes includes*

**Autoimmune polyendocrinopathy syndromes:** The term APS refers to a group of rare endocrine diseases characterized by autoimmune activity against more than one endocrine organ, with possible additional involvement of non-endocrine organs. Autoimmunity is typically directed against different target antigens in different tissues. The two more common autoimmune polyendocrine syndromes, APS type 1 and type 2, have a strong genetic background and have Addison's disease as a major feature. The group furthermore includes APS type 3 and type 4.

The APS type 1 is a rare recessive autosomal disease, also named APECED syndrome (OMIM 240300), and related to *AIRE* gene mutations. Because of a founder effect, APECED is particularly prevalent in Finland (1:25000) but is observed worldwide with variable prevalence[15]. Diagnosis is classically based on presence of at least two out of three "majors" criterions of Whitaker's triad (chronic mucocutaneous candidiasis, autoimmune hypoparathyroidism and adrenal insufficiency or Addison disease). *AIRE* gene (21q22.3), coding for the *AIRE* transcription factor, is involved in immune tolerance mechanisms and contributes to the negative selection of autoreactive T lymphocytes in the thymus, lymph nodes and spleen. AIH and hepatitis as an APECED component may be distinguished on the basis of a different autoantibody profile. The anti-LM antibodies are specific of AIH, which develops in individuals with APECED.

The major target autoantigen of anti-LM antibodies has been documented as the CYP1A2[8,12,14]. In the considered period, we have found four papers reporting in all six patients with APECED syndrome and AIH, that is non-endocrine complication[7,16-18].

The girl described by Huibregtse *et al*[7] had homozygous 967-979del13bp mutation. Meloni *et al*[17] described a longitudinal cohort study in which AIH was seen in 27% of their APS1 Sardinian patients. There are five female patients with a median age of 6.5-year-old and one male of 12-year-old. The course of AIH varied from chronic moderate/severe hepatitis to fatal forms (in two Sardinian and one Indian children) [17,18].

They noted predominance in females, presence in all AIH patients of R139X homozygotes and *HLA-DRB1*0301-DQB1*0201* combination plus LKM autoantibodies (anti-CYP1A2), onset in infancy/childhood, a hitherto unreported predilection for hepatitis and that AIH can be the initial manifestation of APS1. Then they concluded that the role of HLA, in addition to the R139X *AIRE* variant, could influence the APS1 phenotype. Therapy for severe AIH consisted of oral prednisone, tapered off in about 6 mo, and azathioprine, that was continued for years.

In the review of Gatselis *et al*[8], published in 2015, the AIH associated with APECED is considered a component of this syndrome, that the authors described as a third type of AIH, because of the presence of characteristic autoantibodies, such as ANA, anti-LC, anti-LKM, anti-LM.

This review is not included in our listed papers, because of the lack of the established inclusion criteria, but it was interesting for improvement of information about this syndrome. In 2016, Sorkina *et al*[19] described an interesting 4-year-old patient with *AIRE* mutation and AIH, but their diagnosed criteria are not reported; for this reason we exclude the paper in this review. The authors concluded that regular screening for autoantibodies can help identify higher risk for development of AIH.

**Table 3 Group-3: Association not directly related to the disease causative mutation**

| Genetic syndrome | Inheritance | Gene | Ref. | Number of AIH cases | Sex | Age at diagnosis | Nucleotide variant | Protein variant | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| NS | AD | *PTPN11* | Quaio *et al* [38], 2012 | 1 | M | 19 yr | c.[836A>G];[=] | p.[(Y279C)];[(=)] | Alive |
| | | | Loddo *et al*[5], 2015 | 1 | F | 6 yr | c.[923A>G];[=] | p.[(N308S)];[(=)] | Alive |
| WD | AR | *ATP7B* | Ganesh *et al* [40], 2017 | 1 | M | 6 yr | c.[2906G>A];[2906G>A] | p.[(R969Q)];[(R969Q)] | Alive |
| | | | Santos *et al* [41], 2019 | 1 | F | 25 yr | N.R. | N.R. | Alive |
| H syndrome | AR | *SLC29A3* | Bloom *et al* [42], 2017 | 1 | M | 17 mo | c.[1087C>T];[1087C>T] | p.[(R363W)];[(R363W)] | Alive |
| FHL5 | AR | *STXBP2* | Esmaeilzadeh *et al*[43], 2015 | 1 | M | 7 yr | c.[1247-1G>C];[1247-1G>C] | p.[(?)];[(?)] | Death |
| TSC | AD | *TSC1* | Di Marco *et al* [44], 2017 | 1 | F | 47 yr | c.[682C>T];[=] | p.[(R228*)];[(=)] | Alive |
| SCD | AR | *HBB* | Jitraruch *et al* [45], 2017 | 7 | F; M; M; F; F; F; F | 5 yr; 16 yr; 13 yr; 13 yr; 8 yr; 8 yr; 3 yr | c.[20A>T];[20A>T] | p.[(E7V)];[(E7V)] | Alive; Alive; Death; Alive; Alive; Alive; Death |
| | | | Zellos *et al* [46], 2010 | 1 | F | 25 yr | c.[20A>T];[20A>T] | p.[(E7V)];[(E7V)] | Death |
| | | | Hurtova *et al* [47], 2011 | 1 | F | 54 yr | c.[20A>T];[20A>T] | p.[(E7V)];[(E7V)] | Death |
| GD | AR | *GBA* | Ayto *et al*[48], 2010 | 1 | F | 51 yr | c.[1226A>G];[115+1G>A] | p.[(N409S)];[(?)] | Death |
| PLCA | AD | - | González-Moreno *et al* [50], 2015 | 1 | M | 36 yr | NR | NR | Alive |
| | | | Yan and Jin [49] | 1 | F | 50 yr | NR | N.R. | Alive |
| PFIC3 | AR | *ABCB4* | Oliveira *et al* [51], 2017 | 1 | M | 22 yr | c.[874A>T];[3680T>C] | p.[(K292*)];[(I1227T)] | Alive |

AIH: Autoimmune hepatitis; AD: Autosomal dominant; AR: Autosomal recessive; F: Female; M: Male; NR: Not reported; NS: Noonan syndrome; WD: Wilson disease; FHL: Familial hemophagocytic lymphohistiocytosis; TSC: Tuberous syndrome; SCD: Sickle cell disease; GD: Gaucher disease; PLCA: Primary cutaneous amyloidosis; PFIC3: Progressive familiar intrahepatic cholestasis type 3.

**IPEX syndrome:** The IPEX syndrome (OMIM 304790) is a rare X-linked recessive life-threatening disorder characterized by autoimmunity and early death. The causative gene is *FOXP3*. We report four papers and six patients with IPEX syndrome and AIH [20-23]. These patients were hemizygote males of median age of 1.7-year-old. In 2018, Duclaux-Loras R *et al*[20] reported 14% of AIH in a cohort of French IPEX patients. Among these, three patients had AIH with early onset in the first months of life and two died at 8 and 7 mo. In IPEX syndrome the course of AIH is very severe.

**Immunodeficiency, centromeric instability and facial dysmorphism syndromes:** The immunodeficiency, centromeric instability and facial dysmorphism (ICF) syndrome (OMIM 242860) is a rare autosomal recessive immunodeficiency, that involves agammaglobulinemia or hypoglobulinemia with B cells, centromere-adjacent instability of chromosomes 1 and/or 16 (and sometimes 9) in mitogen-stimulated lymphocytes, with facial anomalies and psychomotor delay. Approximately 50 patients have been reported.

It is distinguished in ICF1 correlate to *DNMT3B* gene mutations and ICF2 due to *ZBTB24* gene, ICF3 caused by mutation in the *CDCA7* gene and ICF4 caused by

mutation in the *HELLS* gene. There are two papers which described two patients, one male and one female, with 5 and 3-year-old respectively, affected by ICF1 and ICF2 with AIH[24,25].

**Spondyloenchondrodysplasia with immune dysregulation:** SPENCDI (OMIM 607944) is a very rare autosomal recessive genetic skeletal dysplasia, that may have a heterogeneous clinical spectrum with neurological involvement or autoimmune manifestations. The prevalence is < 1.1000000 and onset is in childhood. In all, we found four patients who have AIH and SPENCDI. In the original article of Briggs *et al* [26], three female patients of 9-year-old, 3-year-old and 6-mo-old have been AIH and SPENCDI, confirmed by homozygous variants in APC5 gene.

In an abstract in Chinese language, for this not included in Table 1, the authors reported a case of a 12-year-old girl with type IIAIH, associated with systemic lupus erythematosus (SLE), treated with methylprednisolone and immunosuppressants, with improvement. Gene sequencing was performed, revealing a compound heterozygous mutations in ACP5 gene. The same paper showed a review of 25 articles (1 Chinese, 24 English) with 74 SPENCDI patients (92%) with autoimmune diseases. They concluded for a strong predisposition to these complications in SPENCDI[27].

**SDS:** SDS (OMIM 260400) is a rare autosomal recessive multisystemic syndrome characterized by chronic and usually mild neutropenia, pancreatic exocrine insufficiency, caused by mutations in the *SBDS* gene. It might be hepatomegaly and liver abnormalities. We found an article which described two patients with SDS and AIH [28].

**Immunodeficiency:** The primary immunodeficiency disorders are a rare heterogeneous group of inherited defects characterized by poor or absent function in one or more components of the immune system. The estimated prevalence of these disorders in the United States is approximately 1:1200 live births[29]. The clinical presentation involves increased susceptibility to infection, chronic diarrhea, failure to thrive, severe and recurrent infections with opportunistic pathogens.

In SCID there is a lack of functional T cells and immune function. We found an article reporting one of two siblings, 12 year-old girl, with SCID, due to homozygous splicing mutation (IVS2-1G>C) in the *CD3γ* gene and AIH[30]. About immunodeficiency syndromes, we want to cite one article, excluded for language, which describe a very rare case of a girl of 18-month-old with chronic granulomatous disease and AIH [31].

### *Group-2 includes*

**Down syndrome:** Trisomy of chromosome 21 (OMIM 190685) is characterized by cognitive impairment, cardiac and gastrointestinal abnormalities and immunodeficiency.

Relevant is also the incidence of autoimmune diseases. Our research found a review in which only two cases with Down syndrome were associated to autoimmune chronic active hepatitis and autoimmune PSC[32]. Because the case reported have been excluded for publication over the years, we evaluated the aforementioned review, which is the only publication in the period considered, that referred to cases of AIH and Down syndrome. The first case was a 29-year-old male, reported by McCulloch *et al*[33] in 1982 while the second was a 21-year-old male with autoimmune PSC by Mehta *et al*[34], in 1995. In 1990, another case of a 12-year-old child is described with Down syndrome and AIH[35]. Considering the known risk of autoimmune complications in Down syndrome, we thought we would find more cases of AIH. On the contrary, literature data showed many cases of viral hepatitis occurring in Down syndrome, due to immunodeficiency condition.

**Other unbalanced genomic diseases:** They are rare genetic syndromes caused by deletion and/or duplication of chromosomes. The correlation of symptoms is variable of cognitive deficit and multiorgan involvement. Monosomy and trisomy for different regions in chromosomes account for about 1% of cases of developmental delay and intellectual disability. Some of them are noted to have immunodeficiency and immune-mediated complications. In our review, we found description of a 24-year-old woman with AIH and SMS (OMIM 182290), due to a 17p11.2 deletions (16,660,721-20,417,975, GRCh37/hg19)[36], another 3-year-old girl patient with 22q13.3 deletion syndrome (Phelan-McDermid syndrome) (OMIM 606232)[37], finally a 12-year-old girl with de novo heterozygous 11.6 Mb chromosome 2q33.1-q34 deletion (197,942,576-209,522,220, GRCh37/hg19)[37].

We think that AIH is due to haploinsufficiency of key genes located in the deleted region. Lymphocyte-specific member of the TNF receptor superfamily (*TACI* gene) located within the SMS region, plays a crucial role in humoral immunity. So we might speculate that *TACI* haploinsufficiency, in this condition, could cause hyperactive B cells and increased capacity for antigen-specific antibody production. In similar manner, the loss of one copy in one or more of the 55 genes, from *NUP50* to *RABL2B*, in 22q13.3 region in Phelan-McDermid syndrome; and of the *CD28/CTLA4/ICOS* gene cluster in 2q33.1-q34 deletion, similar to *ALPS5* due to *CTLA4* haploinsuffiency, would be predisposing AIH. In this case, probably the deletion of the *CD28/CTLA4/ICOS* gene cluster induced a multi-organ inflammation and exhibited a Treg suppressive defect.

### *Group-3 includes*

**NS/RASopathies:** NS (OMIM 163950) is characterized by short stature, typical facial dysmorphology and congenital heart defects. The incidence of NS is estimated to be between 1:1000 and 1:2500 live births. The syndrome is transmitted as an autosomal dominant trait. In more than 50% of patients with NS, mutations in the Protein Tyrosine Phosphatase Non-Receptor Type 11 (*PTPN11*) gene are identified.

We found two patients with the association of NS and AIH. In 2012, Quaio *et al*[38] published the first case of patient with AIH and NS. Another case is a 6 year-old girl, that we reported in 2015, with heterozygous mutation c.923A>G (Asn308Ser) in exon 8 of *PTPN11* gene[5]. Autoimmune diseases and autoantibodies were frequently present in patients with RASopathies, even if the etiopathogenesis is still unknown.

The *PTPN11* are clustered in the interacting portions of the amino N-SH2 (Src homology 2) domain and the phosphotyrosine phosphatase (PTP) domains, which are involved in switching the protein between its inactive and active conformations. Missense mutation causes a gain-of-function changes resulting in excessive *SHP2* activity, that underlie the pathogenesis of NS. We hypothesize that *SHP2* modulates *ERK/MAPK* pathway and its involvement in cytokine/inflammatory signaling. In an interesting article published in 2016, it was highlighted that inhibition of *SHP2* activity blocks T cell proliferation, leading to decreased IFN-γ and IL-17 Levels, ultimately normalizing SLE associated pathogenicity in target tissues. These data suggest SHP2 activity is integrally involved in SLE and that its normalization may be a potent and targeted therapy for treatment of patients with SLE[39].

**WD:** In our research on PubMed, we found two articles about AIH and WD[40,41], that is a disorder of copper metabolism (OMIM 277900). The diagnosis is established by a combination of low serum copper and ceruloplasmin concentrations, increased urinary copper excretion and detection of biallelic *ATP7B* pathogenic variants by molecular genetic testing. The manifestations include neurologic, psychiatric or liver diseases. These include recurrent jaundice, simple acute self-limited hepatitis-like illness, autoimmune-type hepatitis, fulminant hepatic failure, or chronic liver disease. The AIH in WD patients responds well to chelation therapy with D-penicillamine. There were reported a 6-year-old boy and a 25-year-old female patients, presented with clinical symptoms suggestive of AIH, with a mutation in *ATP7B* gene, confirming the diagnosis of WD. In patients who showed chronic hepatopathy resembling AIH, the differential diagnosis with WD is mandatory, because resolving the dilemma allows the clinician to prescribe the appropriate therapy.

**H syndrome:** H Syndrome (OMIM 612391) is an autosomal recessive disorder characterized by cutaneous hyperpigmentation, hypertrichosis and induration with numerous systemic manifestations. The syndrome is caused by homozygous or compound heterozygous mutations in *SLC29A3* a gene on chromosome 10q22 that encodes a nucleoside transporter (hENT3). There is one case report that described a 17 mo-old male with mild to moderate autoimmune chronic active hepatitis, confirmed with biopsy and treated with prednisone and immunosuppressor[42].

**FHL:** In 2015, Esmaeilzadeh *et al*[43] described a patient with FHL5 (OMIM 613101) caused by *STXBP2* gene mutation presenting with AIH. This syndrome is a rare disorder characterized by immune dysregulation, defective function of natural killer cell, proliferation and infiltration of hyperactivated macrophages and T-lymphocytes, cytopenia and hepatosplenomegaly. It was the first description of AIH.

**Tuberous sclerosis complex:** TSC (OMIM 191100) is a rare autosomal-dominant neurocutaneous disorder, with prevalence of 1:6000, characterized by multisystem hamartomas and benign tumors developing. This condition is caused by heterozygous loss-of-function mutations in the *TSC1* or *TSC2* tumor suppressor genes coding for hamartin and tuberin, respectively.

We found an article about a 47 year-old woman, affected by TSC, with a mutation identified in the *TSC1* gene [c.682C>T (p.Arg228*)] and lymphangioleiomyomatosis, sarcoidosis, primary biliary cirrhosis and AIH[44]. This was the first report of this coexistence, and we might speculate that this is related with the dysregulation of the pathway involving *mTOR* and *MAPK* and their interaction.

In literature, *PI3K/AKT/mTOR* signaling has been implicated in SLE pathogenesis. Its activity is increased in SLE mice models as well as in human lupus patients. The expression of this signaling pathway exists broadly in immune cells, including T cells, B cells, monocytes, macrophages, neutrophils and dendritic cells[39].

**Sickle cell disease:** It is a chronic hemolytic disease (OMIM 603903) that may induce acute accidents, like severe anemia, bacterial infections, and ischemic vaso-occlusive accidents caused by sickle-shaped red blood cells obstructing small blood vessels and capillaries. The patients have beta globin variant (Hb S). Our PubMed research found three articles.

In 2017, a retrospective review reported 7 patients of median age of 9 years with sickle cell disease (SCD) and AIH. The patients were treated with standard immunosuppressive therapy[45]. Previous case reports described two patients with SCD and AIH[46,47].

The occurrence of AIH may be due to a complex interaction with the underlying liver disease in altered immunoregulatory mechanisms. AIH is common in patients with SCD and they respond satisfactorily to immunosuppressive treatment. The authors reported how liver biopsy may be helpful in confirming the diagnosis and to exclude acute vaso-occlusive sickling episodes[45].

**Gaucher disease type 1:** It is the chronic non-neurological form of Gaucher disease autosomal recessive (OMIM 230800), characterized by prevalence of 1:100000 organomegaly, bone involvement and cytopenia, caused by a mutation in the *GBA* gene. The hepatomegaly (80% of cases) in rare cases can progress towards fibrosis followed by cirrhosis. We found an article, who described one gaucher disease type 1 patient with autoimmune chronic active hepatitis[48].

**Primary cutaneous amyloidosis:** It refers to a variety of skin diseases characterized by the extracellular accumulation of amyloid. They have genetic heterogeneity and may be caused: Primary cutaneous amyloidosis (PLCA)-1 by heterozygous mutation in the gene encoding oncostatin-M-receptor-beta (*OSMR*) (OMIM 105250), PLCA-2 by heterozygous mutation in the *IL31RA* gene (OMIM 613955), PLCA-3 by mutation in the *GPNMB* gene (OMIM 617920). There were two case reports which described one patient each other, a 36 year-old male and a 50 year-old female, with PLCA and AIH [49,50]. These reports in the literature have been associated to autoimmune disorders, which suggests the possibility of a common underlying immune-mediated mechanism.

**PFIC3:** The PFIC3 is a heterogeneous group of autosomal recessive liver disorders (OMIM 602347), with childhood predominance, which causes cholestasis of hepatocellular, caused by a genetic defect in the *ABCB4* gene. In literature there is the first interesting association of PFIC3 and AIH type 1[51]. It regards a 22 year-old patient with diagnosis of PFIC3 caused by an allele with a previously described mutation and a new genetic variant (c.3680T>C; p.Ile1227Thr), transmitted by his mother, which is associated with AIH. The authors reported the importance of genetic testing of the *ABCB4* gene in patients with autoimmune liver disease with incomplete response to immunosuppressive treatment.

## CONCLUSION

In this review, we performed a research of literature, during the last 10 years, from 2010 to 2020, to collect all clinical cases reporting the association between AIH and genetic syndromes. We observed that AIH is a frequent complication of group-1 syndrome, that includes disease whose causative gene have a role in immunoregulation. AIH is more rarely present in other group of genetic syndromes. If we consider a single disease, the number of articles is very limited, but we suppose that this could be related to rarity of genetic syndrome.

We hypothesize that AIH and genetic syndromes are combination of rare manifestation. Over the last decade, the attention of AIH diagnosis is increased and there is evidence that many triggers are involved for AIH pathogenesis, such as

familiarity, genetic predisposition, drug and infections. This paper suggests that genetic syndromes, as observed in the reported clinical cases, are a trigger for AIH, whose pathogenetic mechanism could be specific for each other, also related to genetic factors.

Genetic syndromes could contribute to the risk of developing AIH with a primitive gene mutation that compromises an immune response. For examples, it is demonstrated role of some gene products such as, *FOXP3*, *ICOS*, *TIGIT*, *CTLA4*, in pro-inflammatory/pro-B helper profile[10].

We suggest that the association between AIH and genetic syndrome might be not casual and claim that there might be an etiopathogenetic correlation between the causative genetic mutation and the immune imbalance, that is expressed as AIH. Considering that we have dealt with rare diseases and sometimes very rare, having found 34 articles in 10 years, we think there are not a few. On the other hand, it is fair to observe that when the clinical cases described are few, it is difficult to exclude that it is a coincidence. Much attention should be paid by clinicians to AIH diagnosis, with periodical autoantibody detection and identification of AIH manifestations and interpretation of liver autoimmune serology, to minimize the problem of underestimation of AIH diagnosis. Moreover, we underly the severity of AIH complication and in these cases the time of diagnosis should be crucial in order to start, as soon as possible, an appropriate therapy.

We suggest that when a patient presents a clinical picture of cryptogenic chronic hepatitis, that is unexplained, it is useful to explore differential diagnosis of AIH associated with genetic syndrome. Given the clinical relevance of this topic, further reports are needed to demonstrate our hypothesis and collect new evidence in this field.

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