Autoimmune hepatitis in monozygotic twins - a case report

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Abstract. – OBJECTIVE: Autoimmune hepatitis is a chronic liver disease caused by a dysfunctional immune system. It is widely believed that autoimmune hepatitis accumulates in families. We found that autoimmune hepatitis does accumulate in monozygotic twins.

CASE REPORT: We present middle-aged monozygotic female twins developing autoimmune hepatitis consecutively within two years. Both twins had developed Graves’ disease and were treated with carbimazole before the onset of autoimmune hepatitis. Both were cigarette smokers. The twins were treated with budesonide and azathioprine, which normalised liver parameters.

CONCLUSIONS: This case report supports the hypothesis that a genetic factor might be of great importance in the aetiology of autoimmune hepatitis.

Key Words: Genetic predisposition to the disease, Twins, Autoimmune hepatitis.

Abbreviations
AIH: autoimmune hepatitis; ALT: alanine transaminase; ANA: antinuclear antibodies; ASMs: anti-smooth muscle antibody; AST: aspartate transaminase; ALP: alkaline phosphatase; CARD10: caspase recruitment domain-containing protein 10; FDRs: first-degree relatives; fT3: free triiodothyronine; fT4: free thyroxine; GD: Graves’ disease; GGT: Gamma-glutamyltransferase (also γGT); GWAS: genome-wide association study; HLA: human leukocyte antigen; IgG: Immunoglobuline G; IgM: Immunoglobuline M; SDRs: second-degree relatives; SLA: anti-soluble liver antigen-antibody; SH2B3: SH2B adapter protein 3; TRAK: TSH receptor antibodies; TSH: thyroid-stimulating hormone.

Introduction
Previous studies have documented autoimmune hepatitis (AIH) clustering in families, but no formal heritability estimates exist. A large family study of patients with AIH, including first-degree relatives (FDRs), second-degree relatives (SDRs), and twin pairs, supported a genetic contribution to this disease¹. Family risk remains low, as the 10-year cumulative risk for AIH is 0.1% in FDRs, and there were no autoimmune hepatitis diagnoses in SDRs¹. Furthermore, monozygotic twin concordance was observed in 1 out of 22 twin pairs, suggesting AIH is a polygenic disease with possibly low penetrance¹.

This case report supports the hypothesis that a genetic factor and an environmental factor (cigarette smoking) might be of great importance in the aetiology of autoimmune hepatitis.

Case Presentation
The 31-year-old twin sister B, with a previously known diagnosis of Graves’ disease (GD) since March 2007 (therapy with carbimazole March 2007- September 2008), visited her general practitioner in October 2011 due to massive occipital hair loss. She is a recurrent smoker who started smoking cigarettes as a teenager and still smokes 5-6 cigarettes a day. After being transferred to the dermatologic department because of clinical evidence of alopecia areata of the ophiasis type, a steroid shock therapy was carried out for 14 days (prednisone 100 mg/day for three days, then taper off) and zinc 60 mg /day due to the pronounced findings, was also introduced. Due to the increased TRAK (TSH receptor antibodies -3,313 IU/L-) that was double the normal limit (<1.8 IU/L) a thyroid ultrasonography was performed in January 2012. There was a reduction in the thyroid volume with normal perfusion compared to the previous findings from 2008 without evidence of an active GD. The thyroid values (Figure 1) have always been normal in the past few years. The patient had
no symptoms in the thyroid area, and in particular, no dysphonia, dysphagia, or dyspnea. In 2020, there were increased transaminases – aspartate transaminase (AST) (Figure 2) and alanine transaminase (ALT) (Figure 3) – 4x the upper norm and increased gamma-glutamyltransferase (GGT) (Figure 4) – 10x the upper norm. The alkaline phosphatase (ALP) (Figure 5) was 3x the upper norm. Albumin (Figure 6) and the overall bilirubin (Figure 7) remained normal. The patient never had hepatitis, while her twin sister developed autoimmune hepatitis two years before. There was no evidence of viral hepatitis, storage disease, dysthyroidism, or sprue in the serological analysis. The serological constellation with increased ANA, IgG, IgM and smooth muscle antibodies indicated an autoimmune-unmediated hepatopathy. The liver biopsy in April 2020 confirmed an overlap syndrome autoimmune hepatitis/primary biliary cholangitis. A therapy with budesonide 9 mg and ursodeoxycholic acid 2x 450 mg daily was established. Two months later, in April 2020, treatment with azathioprine 50 mg daily was started. In August 2020, the dose was increased to 100 mg.

**Figure 1.** Changes of TSH, fT4, and fT3 over time.
daily due to a slight increase in liver function tests and the budesonide was reduced to 6 mg daily in November 2020 and tapering off in March 2021. In June 2021, there was normal liver sonography. Under the existing therapy, AST (Figure 2), ALT (Figure 3) and ALP (Figure 5) have been near normal ever since. The patient received a complete hepatitis A/B vaccination (March, May and October 2020).

The twin sister A presented to the family doctor’s practice in January 2012 due to tiredness, occasional palpitations and increased sweating. She also started smoking cigarettes as a teenager and smokes 5–10 cigarettes per day.

Hyperthyroidism (Figure 1) was shown in the laboratory and GD could be clinically (minor exophthalmos, periorbital soft tissue swelling, positive von Graefe’s sign, conjunctival injection), chemically (TRAK positive), and sonographically confirmed (goitre, hypervascularisation). A treatment with 20 mg of carbimazole daily was established, which was reduced to 15 mg daily after six months with a clear regression of the symptoms and the thyroid hormone profile - thyroid-stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) (Figure 1). In February, May and November 2017, the liver sonography was normal. In January 2018, the diagnosis of autoimmune hepatitis type 1 was confirmed. AST (Figure 2), ALT (Figure 3) and GGT (Figure 4), were increased. ALP (Figure 5), albumin (Figure 6) and overall bilirubin (Figure 7) remained normal. The therapy was carried out with budesonide 9 mg daily (a trial dose reduction in February 2018 for three weeks) and azathioprine 50 mg daily, calcium 500 mg and vitamin D3 400 IE. After increasing the dose of azathioprine to 75 mg daily in August 2018 (under-treated according to the 6-TGN level in July 2018), the transaminases AST (Figure 2) and ALT (Figure 3) normalised. The liver sonography showed no abnormalities. In April 2019, there was a further dose reduction of budesonide to 3 mg daily and after tapering off budesonide in June 2019, transaminases AST (Figure 2) and ALT (Figure 3) remained normal.
Figure 3. Change of ALT over time.

Figure 4. Changes of γ-GT.
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Until October 2019, a complete hepatitis A/B immunisation also took place. In March 2021, the subclinical hypothyroidism remained stable under the monotherapy with azathioprine 75 mg daily (see Figure 7).

The diagnosis of osteopenia was made in both twin sisters by using osteodensiometry (A 03/2018, B 01/2021). Both twins receive substitution therapy with calcium and vitamin D3. Both stopped smoking in 2014.

Discussion

This case report describes monozygotic female twins developing AIH within two years. Both twins had developed GD before AIH.

AIH is an uncommon autoimmune liver disease of unknown aetiology which tends to develop in middle-aged women. The disease has an approximate prevalence of 17 per 100,000. It is characterised by chronic destructive inflammation within the liver parenchyma, elevated serum transaminase levels (AST and ALT), autoantibody-positive for the anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-soluble liver antigen-antibody (SLA) and elevated serum IgG level, which usually exceeding 2000 mg/dl. In particular, IgG levels are sometimes low in the early stages of acute-onset cases.

Evidence suggests a significant involvement of autoimmunity, but the onset mechanism of AIH is still unclear. Additionally, AIH might develop due to environmental trigger factors, such as drug exposure and viral hepatitis, with the host’s genetic predisposition in the background of the disease process. Although the risk of familial AIH is not significant, cases of familial onsets have frequently been reported. This shows that autoimmunity is not the only mechanism involved and highlights the importance of genetic predisposition and environmental factors.

The genetic factors that determine a person’s susceptibility to AIH have not been fully explained yet. Nonetheless, the human leukocyte antigen (HLA), which is the primary antigen presentation molecule, is known to be the most important genetic factor associated with AIH onset.

Environmental degradation in genetically susceptible individuals may result in abnormal immunological reactions and lead to autoimmune-mediated hepatocyte injury. Although the risks of AIH in the family are relatively low, familial aggregation of AIH has been frequently reported. This highlights the significance of genetic determinants and environmental triggers.

Numerous susceptible loci for AIH in the human leukocyte antigen (HLA) and non-HLA region have been identified. A genome-wide association study (GWAS) in the Netherlands determined HLA-DRB1*0301 and DRB1*0401 as the most relevant susceptible genotypes for AIH. Simultaneously, SH2B3 and CARD10 (genes in the non-HLA region) were significantly associated with AIH.

A well-designed case-control study is warranted to find and identify environmental triggers in lifestyle, food, and beverages, or in chemicals, antibiotics, and xenobiotics, which trigger innate and adaptive immune responses leading to a breakdown of tolerance against hepatocytes.

Graves’ disease may lead to hepatic dysfunction due to the direct effect of increased thyroid hormone circulation. The liver and the thyroid functionality are closely intertwined. Thyroid hormones (fT3 and fT4) are essential parts of the hepatic function regulation, while the liver participates in the metabolism of thyroid hormones.

Thyroid hormones are glucuronidated and sulfated in the liver. Therefore, an excess of thyroid hormones can cause hepatocyte injury. In studies in animals demonstrated that excess T3 induces hepatocyte apoptosis and causes liver dysfunction. Hepatic dysfunction in hyperthyroidism can be caused by the hyperthyroidism itself, heart failure resulting in hepatic venous congestion, or associated liver disease. A cholestatic pattern with elevated alkaline phosphatase and bilirubin may also be seen in hyperthyroidism.

Elevated liver enzymes are not a contraindication to anti-thyroid drugs. Among anti-thyroid drugs, methimazole is the preferred agent in treating hyperthyroidism as it is associated with less severe hepatic toxicity.
Figure 5. Changes of ALP over time.

Figure 6. Change of albumin over time.
Conclusions

Our case report provides additional hints to a possible genetic susceptibility or at least genetic vulnerability for autoimmune hepatitis combined with external factors, such as cigarette smoking and anti-thyroid drugs.

Conflict of Interest
The authors declare that they have no competing interests.

Informed Consent
Both patients gave their informed consent for data analysis and publication of the case report.

Consent for Publication
Both patients provided written consent for the publication of this case report and any accompanying images.

Availability of Data and Materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Authors’ Contributions
KW drafted the manuscript. VCS performed the data processing and statistical analyses and BK helped draft the manuscript. All authors approved the final version.

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Figure 7. Changes of bilirubin over time.


