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CASE REPORT

Pharmacogenetic aspects of therapy for autoimmune hepatitis against the background of degenerative-dystrophic joint lesions

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ABSTRACT

Introduction and aim. The pathogenesis of autoimmune diseases, including musculoskeletal, gastrointestinal, and endocrine manifestations, involves the interaction of genotype and environmental factors. Pathologies demonstrate comorbidity and clinical heterogeneity even within a single family. Genetic polymorphisms of one-carbon metabolism are key regulators of cellular processes that become therapeutic targets.

Description of the case. The study describes personalized therapy for a patient with an autoimmune comorbid disease, with an emphasis on genetic and metabolic characteristics. The treatment regimen is adapted to the features of the one-carbon metabolism profile of a patient with chronic autoimmune hepatitis and degenerative-dystrophic joint disease. Family history includes autoimmune thyroiditis, vitiligo, Parkinson's disease, cardiovascular diseases. The patient's genotype for single nucleotide polymorphisms rs1801133, rs1801131, rs1801394, rs1805087, and rs3733890 of the one-carbon metabolism genes is associated with elevated plasma homocysteine levels. After treatment, changes in biochemical parameters were observed: alanine aminotransferase (72→53 U/L), aspartate aminotransferase (53→44 U/L), gamma-glutamyltransferase (129→89 U/L), alkaline phosphatase (313→125 U/L) and homocysteine (15.1→17.0 μmol/L).

Conclusion. Positive dynamics after personalized therapy demonstrates the importance of an interdisciplinary approach to etiopathogenetic treatment, emphasizing the need to support hepatobiliary function along with muscular and skeletal therapy.

Keywords. autoimmune hepatitis, betaine-homocysteine methyltransferase, one-carbon metabolism genes, personalized therapy

Introduction

Personalizing pharmacotherapy for patients, especially for severe chronic noncommunicable diseases, is a global and, in particular, European trend. The main focus in practical activities is the application of the results of pharmacogenetic studies and the accumulated experience in this area to predict therapeutic and side effects, the consequences of the interaction of several simultaneously prescribed drugs, and improving treatment outcomes. The implementation of prediction is based primarily on

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knowledge of the patient's genetic profile. At the same time, it is necessary to take into account a large amount of patient data on other biological and environmental parameters such as life and family history.[1,2]

The development of molecular types of analysis has created opportunities for early assessment of pleiotropic effects of mutations and the development of individual treatment methods for patients, in particular, with autoimmune diseases, which at the same time may have clinical manifestations from the endocrine musculoskeletal, gastrointestinal tract, and other systems.[2-6] Common foundations and mechanisms of disease pathogenesis involve a complex interaction of genetic, embryological, immunological, and exogenous factors.[7] For example, autoimmune polyendocrine syndrome (APS) includes a diverse group of clinical conditions and is characterized by functional impairment of many endocrine organs due to loss of immune tolerance.[8-10] Autoimmune thyroiditis is associated with stomach disorders in 10–40% of patients.[7-10] Patients with type 1 diabetes often have concomitant multisystem autoimmune diseases, including thyroid, parathyroid gland pathologies, celiac disease, vitiligo, gastritis, dermatoses, and rheumatic diseases.[2]

Genetic studies of autoimmune diseases allow exploring pathogenesis and drug efficacy. It has been established that genetic factors of autoimmune hepatitis coincide with factors of other autoimmune diseases. Certain ethnic features regarding candidate genes and alleles predisposing to autoimmune hepatitis in Europeans, Latin Americans, and Japanese are presented.[11] Authors note that the results of genetic studies explain the phenotypic heterogeneity of autoimmune hepatitis and identify biological markers of drug response. The polymorphism of some genes associated with the pharmacokinetics and pharmacodynamics of drugs can modify the gene expression, causing changes in treatment in patients with autoimmune diseases.[12]

One-carbon metabolism potentially plays a role in the regulation of homeostasis and is also a target for drugs that affect the digestive system and metabolism processes of antineoplastic, antiepileptic, and other drugs.[13-19] Certain genotypes for one-carbon metabolism genes, particularly the *MTHFR* gene, may predispose to increased levels of circulating homocysteine, causing inflammation through oxidative stress. Resulting vascular dysfunction affects tissue function, leading to the development of cardiovascular, cerebrovascular, thromboembolic diseases, inflammatory syndromes, and neurodegenerative pathologies. An increase in homocysteine levels is observed in various liver diseases, including metabolically associated fatty liver disease. Hyperhomocysteinemia is noted in patients with rheumatoid arthritis. A link between hyperhomocysteinemia and complications of diabetes has been established since patients with diabetic angiopathy had high homocysteine levels.[20-25]

One pathway of homocysteine conversion to methionine is provided by betaine-homocysteine methyltransferase (BHMT). Certain genotypes for the *BHMT* gene may provide normal or reduced enzyme activity.[26] Under the appropriate genotype, maximum expression of BHMT is observed with a diet low in methionine but high in methyl donors such as betaine, choline, or betaine sulphonium analogs. Betaine functions as an osmolyte and methyl group donor, with its main physiological effects studied in animals and humans, especially against the background of complex therapy for hepatobiliary system pathology including hepatocellular carcinoma.[27-31]

Over the last decades, the literature widely discusses the experience of successful simultaneous use of drugs from different pharmacotherapeutic groups, in particular, corticosteroids, lipotropic substances used in liver diseases, drugs that affect the digestive system and metabolic processes, amino acids and their derivatives, including autoimmune pathologies of the hepatobiliary system.[32-35] At the same time, it is advisable to take into account the genetics of drug metabolism in patients with comorbid pathology against the background of the appointment of complex therapy, which can provide support for clinical decisions to improve medication management in medical care. Despite the universality of many aspects of genetic information, it is important to study the practical experience in each country or region, considering the ethnic, sociocultural and other characteristics of patients and the environment.[36]

For example, the diet may involve products that interact with different effects with the same enzymes as the prescribed drugs.[37] Therefore, personalization of complex therapy based on the analysis of the genotype and other features of the comorbid patient with autoimmune pathology is relevant.

Aim

The study aims to analyze the possibility of an individual approach to treatment, taking into account the genetic and metabolic characteristics of a patient with comorbid autoimmune pathology and degenerative-dystrophic joint lesions.

Description of the case

The patient D., Eastern European male, 53 years old, was observed and underwent treatment at the municipal non-commercial enterprise "City Clinical Hospital No. 13" of the Kharkiv City Council and the municipal non-commercial enterprise "City Multidisciplinary Clinical Hospital No. 17" of the Kharkiv City Council, Kharkiv, in 2021–2024.

Laboratory and instrumental investigations were carried out.[38,39] Laboratory studies, including general clinical, biochemical, immunological, and molecular genetics

were performed using samples of blood, urine, and feces. General clinical biochemical, immunofermentative, immunofluorescent, electrochemiluminescence, PCR qualitative types of analysis were conducted using analyzers Mindray BC-3000 Plus (Mindrey), Cobas 8000/Cobas Pro/Cobas6000/Cobas e411(Roche Diagnostics), Euroimmun Analyzer I Eurostar III Plus, and a fluorescent microscope (Euroimmun). Molecular-genetic analysis of polymorphic variants C677T (rs1801133) and A1298C (rs1801131) of the *MTHFR* gene (OMIM: 607093), A2756G (rs1805087) of the *MTR* gene (OMIM: 156570), A66G of the *MTRR* gene (rs1801394) (OMIM: 602568), G742A (rs3733890) of the *BHMT* gene (OMIM: 602888) was carried out by PCR-RFLP using Thermal Cycler Biometra T3000 (Biometra).[16,17,40]

Instrumental methods included ultrasound examination (Philips Clear Vue 550, Philips), multislice computed tomography (Philips Brilliance 64, Philips), electrocardiography (Heaco 300 G; Heako), radiography. A clinical-genealogical analysis allowed obtaining and studying data on relatives of the first to third degrees of kinship.

The presented work is done in accordance with the main positions of the "Rules of Ethical Principles for Conducting Scientific Medical Research Involving Human Subjects" adopted by the Helsinki Declaration (1964-2013), ICH GCP (1996), EEC Directive No. 609 (11/24/1986), Orders of the Ministry of Health of Ukraine No. 690, No. 944, No. 616. The patient in our project was informed about the purpose, design, methods of the study and provided written informed consent to be a participant in this completely anonymous project.

We provide an example of using genetic testing results for an individual approach to pharmacotherapy of a comorbid patient with autoimmune pathology.

Anamnesis

The patient has a main diagnosis: autoimmune hepatitis (ANA 1:320) with minimal activity cytolytic and cholestatic syndromes. Hemangioma of the right part of the liver (d up to 1cm). Comorbid diagnosis: Systemic involvement of connective tissue, unspecified. Bilateral deforming gonarthrosis II-III stages, arthrogenic contracture of both knee joints. Deforming arthrosis of the acromioclavicular joint 1–2 stages right side. Sclerosis of the large tubercle of the right shoulder bone with impairment of the right upper limb. Mixed contracture of the right shoulder joint. Osteoarthritis of the lumbar spine, spondyloarthrosis. Impaired joint function I stage. Pain syndrome. Chronic recurrent urticaria. Vitiligo. Alopecia. chronic atrophic autoimmune gastritis, *Helicobacter pylori* negative, in the acute stage. Post-arthroscopy state of the left knee joint, right knee joint, varicocele.

The family history of the patient is burdened with autoimmune thyroiditis, vitiligo, Parkinson's disease, and cardiovascular diseases, including varicose veins, hypertensive disease, myocardial infarction in relatives of 1–3 degrees of kinship. Does not smoke or drink alcohol.

The patient has been suffering from vitiligo since childhood, chronic urticaria for more than 18 years, arthrosis for more than 15 years. Due to arthralgia, he repeatedly turned to the trauma department, where diagnostic and therapeutic measures were carried out.

The general condition of the patient is of moderate severity, consciousness is clear, position is active. Skin and visible mucous membranes are pale pink, moist. Height 184 cm, weight 100 kg. Body mass index (BMI) – 29.5 kg/m^3. Peripheral lymph nodes are not palpable. In the lungs, breathing is vesicular, no rales. Heart tones are muffled, rhythmic. Blood pressure (BP) – 140/90 mm Hg Art., HR=Ps=70 bpm. Tongue moist, coated with a dense white-yellow plaque. The abdomen on inspection is symmetrical, no hernial protrusions, actively participates in the act of breathing, on superficial palpation painless, unstrained, peritoneal symptoms negative, Mendel's symptom negative, on methodical deep sliding palpation by Obraztsov-Strazhesko – the abdomen is soft, painless. The liver is not palpable; the edge of the liver is soft, painless, smooth. Dimensions of the liver by Kurlov 12×11×10 cm. Tenderness at the points of Mayo-Robson and Kacha is absent; tenderness in the zone of Schoffar is absent. The spleen is not palpable. Pasternatsky's symptom is negative on both sides. Stool daily formed without pathological admixtures, diuresis – urine of normal color, urination free, painless. Peripheral edema – no.

Joints: sizes and shapes are changed, mobility impaired. Pain on palpation and movement.

Laboratory study data

Analysis of laboratory test results in dynamics, before and after treatment, are within the average reference values for general blood test, electrolytes, proteinogram, lipidogram, with the exception of Low-density lipoproteins (LDL) (1.37 mmol/L, 1.68–4.53) and High-density lipoproteins (HDL) (0.82 mmol/L, 1.04–1.55). The results of laboratory studies in dynamics are presented in Table 1.

Indicators of general clinical analysis of urine, microscopic and physico–chemical properties are within the norm. Ketone bodies not found. No bacteria. Urine analysis for diastase – 166 U/L against the norm of 0–450 U/L. Coprogram without pathological deviations. Stool analysis for ova/helminths – not found. Pancreatic elastase in feces – 720 μg/g against a norm of more than 200 μg/g.

Table 1. Results of laboratory tests of the patient

Indicator	Result before treatment	Result after treatment	Reference values
Biochemical blood test			
Blood albumin, g/L	43	52	35–50
Thymol test, units	2.2		up to 4
Total bilirubin, μmol/L	15.9	10.4	5–21
Bilirubin direct, μmol/L	5.4	4.0	2.20–5.13
Bilirubin indirect, μmol/L	10.5	6.4	6.3–15.4
Alanine aminotransferase (ALT), U/L	72	53	0–41
Aspartate aminotransferase (AST), U/L	53	44	0–37
Gamma-glutamyl transferase (GGT), U/L	129	89	0–55
Alkaline phosphatase (ALP), U/L	313	125	53–128
Alpha-amylase, U/L	87	34	20–104
Creatinine, μmol/L	78.4	93.3	38.8–93.2
Calurea, μmol/L	5.3		0–8.3
Blood glucose, mmol/L	5.76	5.76	4.11–5.89
Homocysteine, μmol/L	15.1	17.0	up to 15.0
Serum iron, μmol/L	22.2		11.6–31.3
Transferrin, g/L	3.0		2–3.6
Ferritin (FER), μg/L	108.0		30–220
Ceruloplasmin, mg/dL	19		15–30
Rheumatic tests			
C-reactive protein, mg/l	up to 0.6		up to 6
Rheumatoid factor, IU/ml	negative		up to 12
Antistreptolysin-O, IU/ml	81		up to 200
Coagulogram (Coagulation tests)			
Prothrombin time, seconds	11.7		12–18
Prothrombin index, %	107		90–105
International normalized relationship (INR)	0.92		0.85–1.15
Prothrombin index according to Quick, %	129		70–130
Activated partial thromboplastin time (APTT), s	27.9		24–34
Blood test for hormones			
Thyroid stimulating hormone (TSH)	2.0		0.3–4
Immunological tests			
Autoimmune panel STD-X, serum (Ro/SS-A 52, La/SS-B, CENP-B, Scl-70, dsDNA, Jo-1, MPO, PR3, AMA M2, LC 1, LKM 1, PM/Scl 100, SRP 54, Sp 100, gp 210, Ku, Sm, U1-snRNP), kU/L	0.18–0.28		<0.3 – negatitve result
Antibodies IgG SS-A-52 (Ro-52), SS-A-60 (Ro- 60), SS-B (La), RNP/Sm, RNP-70, RNP-A, RNP-C, Sm-BB, Sm-D, Sm-E, Sm-F, Sm-G, Scl-70, Jo-1, dsDNA, ssDNA, polynucleosomes, mononucleosomes, complex histones, histone H1, H2A, H2B, H3, H4,Pm-Scl-100, centromeres B	3.0		<1.0 – negative result
Antinuclear antibodies (ANA)	1:320		<1:100 – negative result
Parietal cells of the stomach, antibodies IgG (PCA)	2.45		<1.00 – negative result
Analysis for HbS Ag and anti–HCV			
Hepatitis B	Not found		Not found
Hepatitis C	Not found		Not found
Genetic tests			
MTHFR			
C677T	CT		CC. CT. TT
A1298C	AC		AA. AC. CC
MTR			
A2756G	AG		AA. AG. GG
MTRR			
A66G	AG		AA. AG. GG
BHMT			
G742A	GG		GG. GA. AA

Data of instrumental studies

Electrocardiogram (ECG): HR=55 bpm. Sinus rhythm. Left ventricular myocardial hypertrophy.

Ultrasound of abdominal organs

The liver is not enlarged. Right lobe KBP 157 mm. Left lobe thickness 114 mm KKP 74 mm. Contours are even, clear, edge sharp. Parenchyma is homogeneous, finely granular, increased echogenicity. Hyperechoic formation in SgV up to 1 cm in d. The gallbladder is enlarged V=49 cm^3. Deformed due to the septum in the neck. Walls thickened to 28 mm. In the lumen, homogeneous bile. Hepatocholedochus is not dilated 0.4 cm in d, walls are not thickened. The pancreas is well visualized, not enlarged, head 30 cm, body 21 cm, tail 28 cm. Wirsung's duct is not dilated – 1 mm. Contours are clear, even. Echogenicity is normal. Structure is homogeneous. Portal vein 0.95 cm in d, splenic vein 0.8 cm in d, periportal fibrosis absent. Morrison's pouch does not contain fluid. The spleen is not enlarged 1.08x0.54 cm. Echogenicity is normal. Kidneys are typically located, shape unchanged, mobility sufficient. Right kidney 1.09x0.62 cm. Left kidney 1.27x0.59 cm. Contours are even, clear. Parenchyma is homogeneous, parenchyma height not reduced (right 21 mm, left 23 mm). Cavity system unchanged. Conclusion: Diffuse changes in liver parenchyma of the type of steatosis II stage. Hemangioma of the right lobe of the liver.

According to the Revised Original Score for Autoimmune Hepatitis (AIH), a pre–treatment score of 10 or greater and a post–treatment score of 12 or greater indicates "probable" AIH. A pre–treatment score of 10 has a "sensitivity" of 100%, a specificity of 73%, and a diagnostic accuracy of 67%. The patient's total pre–treatment score was 12.

Prescribed treatment

Therapy was prescribed in accordance with the Ukrainian clinical protocol for providing medical care to patients with autoimmune hepatitis, international recommendations Practice Guidance and Guidelines and manufacturers' instructions.[38,39] Basic therapy – budesonide, 9 mg per day, additional therapy – ursodeoxycholic acid, 1000 mg per day, ademetionine, 1000 mg per day, betaine 2 g per day. The patient is recommended to continue the prescribed therapy for up to two months. Against the background of the therapy, positive clinical and laboratory dynamics are observed.

Discussion

Interactions between drugs affect the effectiveness of therapy and the possible toxicity of active substances, after which the absence of the expected therapeutic result and unpredictable side effects may be observed. Taking into account the features of the simultaneous use of drugs and their interactions is important for pre-

dicting the results of treatment and preventing negative events.[41]

The metabolism of budesonide is mediated by the CYP3A4 enzyme, as well as CYP3A5 and CYP3A7.[42] Accordingly, the need for simultaneous use of inhibitors, inducers or substrates of CYP3A4 requires an assessment of the risk of systemic side effects and dose adjustment of the drugs. Ursodeoxycholic acid (UDCA) is an inducer of P450 3A. At the same time, according to the manufacturer's instructions, induction is not observed when interacting with budesonide.

According to the literature, it is known that combination therapy with ursodeoxycholic acid and budesonide was more effective than ursodeoxycholic acid monotherapy for primary biliary cirrhosis–autoimmune hepatitis overlap syndrome. In addition, budesonide has fewer side effects, for example, compared to prednisone.[33] Another potential long-term benefit of budesonide therapy is the preservation of bone mineral density.[39] Results from several studies suggest that combination therapy with ursodeoxycholic acid + [corticosteroids and/or antimetabolites] may be superior to ursodeoxycholic acid and corticosteroids ± azathioprine for the treatment of autoimmune hepatitis-primary biliary cirrhosis, but the authors clarify that further studies are needed to definitively demonstrate this.[32] Results of the simultaneous use of UDCA and budesonide are more effective than UDCA and placebo.[34]

S-adenosyl-L-methionine (SAMe) is known to be a hepatoprotector related with methylation. Also SAMe has been shown to suppress autoimmune reactions in PBC. The authors suggest potential therapeutic applications of SAMe.[43]

Data on the combination therapy of ursodeoxycholic acid and S-adenosyl-L-methionine in the treatment of gestational cholestasis are presented in the EASL Clinical Practice Guidelines on the management of liver diseases in pregnancy 2023.[35]

In vitro, SAM and betaine have been shown to enhance the antiviral effects of PegIFN-alpha-2a/2b and ribavirin. Both substances positively affect interferon-induced gene expression in individuals with viral hepatitis who do not respond to pegIFNα/ribavirin. SAM prevents CCl4-induced liver cirrhosis, inhibits cancer growth, and has a pro-apoptotic effect on hepatocellular carcinoma and MCF-7 breast cancer cells.[29] Combinations of SAMe with taurine and/or betaine have hepatoprotective effects against ethanol-induced liver damage and antioxidant functions in addition to anti–inflammatory effects against bacterial and/or viral inflammation.[30,31] Thus, the addition of ursodeoxycholic acid, ademetionine, and betaine to basic budesonide therapy potentiates positive dynamics.

When planning the treatment regimen, the patient's genetic and metabolic features were taken into account.

From the manufacturer's instructions for ademetionine, it is known that a contraindication to its prescription is genetic defects affecting the methionine cycle and/or causing homocystinuria and/or hyperhomocysteinemia during ademetionine therapy. Because the patient's genotype for five SNP genes of one–carbon metabolism – *MTHFR* 677CT/*MTHFR* 1298AC/*MTR* 2756AG/*MTRR* 66AG/*BHMT* 742GG, it may predispose to increased levels of homocysteine in the blood plasma.

It is known that heterozygous genotypes for the main genes of folate/methionine metabolism are associated with the highest indicators of homocysteine content in blood plasma.[22–24] Given such a genotype, it is advisable to conduct a study of the homocysteine level in the blood plasma. Before treatment, the indicator was 15.1 μmol/L against a reference value of 15 μmol/L (Table 1). Considering that the patient has a homozygous genotype G742G for the functional allele rs3733890 of the *BHMT* gene, the prescription of a dietary supplement with betaine and arginine will promote the remethylation of homocysteine into methionine and prevent an increase in homocysteine levels. Since hyperhomocysteinemia is an independent risk factor for cardiovascular and other pathologies for a patient with a burdened family history and own diseases, its prevention is particularly relevant. Therefore, the combined prescription of ademetionine with a dietary supplement with betaine and arginine is rational, with which changes in biochemical indicators in dynamics were noted: ALT (72 and 53 U/L), AST (53 and 44 U/L), GGT (129 and 89 U/L), ALP (313 and 125 U/L), homocysteine (15.1 and 17 μmol/L) (Table 1). The dynamics of homocysteine are not statistically significant.

The role of betaine as a dietary supplement in the prevention/mitigation of liver diseases associated with metabolic disorders and alcohol consumption is considered well–studied.[44] Betaine therapy alone has been shown to prevent vascular events in homocystinuria and also has benefits in other conditions associated with hyperhomocysteinemia as adjunctive therapy. Since betaine increases the level of methionine, reducing and maintaining the level of homocysteine is possible and effective with a diet limiting methionine and dietary supplements with betaine.[45,46] When planning a diet, it is also advisable to consider the needs for B vitamins, as well as other metabolic features associated with pathologies of the gastrointestinal tract and bone tissue according to the genotype.[47] Patients who have been taking dietary supplements with betaine for a long time should monitor the level of methionine and homocysteine in blood plasma.

Since recommendations regarding the diet must take into account the peculiarities of all drugs metabolism during treatment, and the peculiarities of drug–food interactions, it is important to note that budesonide

is a substrate of the cytochrome P450 3A4 isoenzyme CYP3A4. A drug or product that alters CYP3A4 activity may increase or decrease budesonide levels in the body. For example, grapefruit is a potent CYP3A4 inhibitor and may increase systemic exposure to budesonide.[48] Seville oranges, often used to make orange marmalade, pomelo, and tangelo may have the same effect as grapefruit juice. In addition, ursodeoxycholic acid is an inducer of P450 3A. Consumption of CYP3A4 inhibitors is not recommended during treatment with drugs that are metabolized by this enzyme. It is advisable that dietary advice to patients includes information on undesirable and preferred components and their combinations during treatment and, if possible, taking into account the patient's genotype as a metabolizer.[49]

In addition to understanding the interactions between drugs and products, it is advisable to consider pharmacogenetic and therapeutic recommendations for specific drug-gene pairs to predict treatment outcomes depending on the patient's genetic and metabolic status as a metabolizer. In the presented case, it would be useful to assess the patient's genotype for the CYP3A4 gene, since the two prescribed drugs are metabolized by this enzyme.[49] It would be possible to more accurately predict the therapeutic effect and dosages. At the same time, standard protocols do not involve assessing the patient's genotype before prescribing the mentioned drugs, so we consider such a project as promising.

We have not found data in the literature on the combination in patients of autoimmune hepatitis and arthrosis, although joint pain is a symptom of both autoimmune hepatitis and diseases of the musculoskeletal system. Provided that the patient's genotype for genes associated with autoimmune hepatitis and arthrosis is unknown, we can discuss the etiology of the patient's multifactorial pathologies using various hypotheses.

Comorbidity may be caused by the pleiotropic effect of one of the genes included in the genetic networks of both pathologies. It is known that genetic features of vitamin D reception are associated with both the development of autoimmune hepatitis and bone tissue disorders. Dysfunctional products of genetic variants or deficient levels of the gene product can disrupt homeostatic mechanisms that affect the proliferation and survival of autoreactive T- and B-cells, regulate the production of cytokines, and modulate inflammatory and immune reactions.[39] Comorbidity may be due to independent genetic causes. In such cases, the clinical picture of the patient reflects the realization of the pathological genotype according to several included genes. For example, we previously described a patient who had mutations in the *HFE and ATP7B* genes associated with the development of two independent monogenic pathologies – hemochromatosis and Wilson's disease.[50]

At the same time, the complex genetic architecture of multifactorial diseases presupposes the implementation against the background of many environmental factors, the contribution of which is difficult to assess. It is believed that exposure to xenobiotics can act as environmental triggers for the loss of autotolerance to autoantigens in individuals genetically predisposed to the development of autoimmune hepatitis.[39] In this regard, it is possible to discuss the effects of doses, duration of administration and the risk of hepatotoxicity of non-steroidal anti-inflammatory drugs, which the patient took against the background of the development of arthrosis.[51] However, we did not set a goal in this work to find out and present the genetic nature of comorbidity in the described patient. Such research requires a different design and technological solutions. Given the multifactorial nature of the described pathologies, assessment of their genetic landscape will probably, but not necessarily, be able to identify candidate genes or genes and may be a continuation of this project.

Considering the patient's comorbidity, during the administration of budesonide for the prevention of osteoporosis, it is suggested to maintain a high calcium intake, from food and supplements – 1500 mg/day, vitamin D – 800 IU/day.[48] Moderate physical activity without strain and lifting heavy objects is recommended. Also, considering the presence of vitiligo and chronic recurrent urticaria in the patient, regular supervision by a family doctor, gastroenterologist, traumatologist, and allergist is recommended. Since thyroid dysfunction and other endocrine aspects may be observed in patients with autoimmune hepatitis and given the burdened family history of autoimmune thyroiditis, consultation with an endocrinologist may be useful. The patient also received dietary recommendations.

The limiting factor in assessing the effectiveness of therapy is the patient's awareness and commitment to follow the instructions not only regarding the drug regimen, but also the diet, activities, daily routine and other components. This problem is international and depends on many factors. At the same time, modern models of specialist–patient partnership involve combining various ways of patient involvement, including care experience and mediation in health care, therapeutic patient education and patient education pathways, as well as patient–professional partnership.[52]

Conclusion

The clinical case demonstrates the appropriateness of personalized therapy in the example of autoimmune hepatitis, taking into account the genetic characteristics of patients that affect metabolism in the context of ademetionine therapy. The appropriateness of involving specialists of various specialties and a complex of research methods for etiopathogenetic treatment is sub-

stantiated. Genotyping an individual for rs3733890 allows specifying the ways of correcting one–carbon metabolism.

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Declarations

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Author contributions

Conceptualization, T. B. and O. F.; Methodology, T. B. and O. F.; Software, S. D. and V. D.; Validation, S. D. and V. D.; Formal Analysis, S. D. and V. D.; Investigation, T. B., V. B. and O. F.; Resources, T. B.; Data Curation, S. D. and V. D.; Writing – Original Draft Preparation, V. D.; Writing – Review & Editing, T. B., V. B., O. F., S. D. and V. D.; Visualization, T. B. and V. B.; Supervision, T. B., V. B. and O. F.; Project Administration, T. B.; Funding Acquisition, no

Conflicts of interest

All author declare have no conflict of interest.

Data availability

Not applicable.

Ethical approval

Patient signed informed consent was taken regarding publishing their data. And the study was approved by the Institutional Ethics Committee.

References

1. Floris M, Moschella A, Alcalay M, et al. Pharmacogenetics in Italy: current landscape and future prospects. *Hum Genomics*. 2024;18(1):78. doi: 10.1186/s40246-024-00612-w
2. Popoviciu MS, Kaka N, Sethi Y, et al. Type 1 Diabetes Mellitus and Autoimmune Diseases: A Critical Review of the Association and the Application of Personalized Medicine. *J Pers Med*. 2023;13(3):422. doi: 10.3390/jpm13030422
3. Conti L, Galli G, Ligato C, et al. Autoimmune atrophic gastritis and coeliac disease: A case–control study. *Dig Liver Dis*. 2023;55(1):69-74. doi: 10.1016/j.dld.2022.07.001
4. Massironi S, Gallo C, Elvevi A, et al. Incidence and prevalence of gastric neuroendocrine tumors in patients with chronic atrophic autoimmune gastritis. *World J Gastrointest Oncol*. 2023;15(8):1451-1460. doi: 10.4251/wjgo.v15.i8.1451
5. Katsumata R, Kamada T, Murao T, et al. A Case of Autoimmune Gastritis and Hepatitis with Enlarging Gastric Polyps after Reducing the Dose of Prednisolone. *Case Rep Gastroenterol*. 2023;17(1):117-123. doi: 10.1159/000529151
6. Kunovsky L, Dite P, Jabandziev P, et al. Autoimmune Diseases of Digestive Organs–A Multidisciplinary Challenge: A Focus on Hepatopancreatobiliary Manifestation. *J Clin Med*. 2021;10(24):5796. doi: 10.3390/jcm10245796
7. Antonelli A, Benvenga S. Editorial: The Association of Other Autoimmune Diseases in Patients With Thyroid Autoimmunity. *Front Endocrinol (Lausanne)*. 2018;9:540. doi: 10.3389/fendo.2018.00540
8. Suzuki A, Hayashi K, Hayashi M, et al. A Case of Autoimmune Polyendocrine Syndrome Type 3B and Peripheral Neuropathy Due to Thiamine Deficiency. *Cureus*. 2024;16(1):e52123. doi: 10.7759/cureus.52123
9. Betterle C, Sabbadin C, Scaroni C, et al. Autoimmune Polyendocrine Syndromes (APS) or Multiple Autoimmune Syndromes (MAS). In: Colao A, Jaffrain–Rea ML, Beckers A. (eds). *Polyendocrine Disorders and Endocrine Neoplastic Syndromes. Endocrinology*. Springer, Cham. 2019. doi: 10.1007/978–3–319–73082–0_1–1
10. Lahner E, Conti L, Cicone F, et al. Thyro–entero–gastric autoimmunity: pathophysiology and implications for patient management. *Best Pract Res Clin Endocrinol Metab*. 2020;34(1):101373. doi: 10.1016/j.beem.2019.101373
11. Higuchi T, Oka S, Furukawa H, et al. Genetic risk factors for autoimmune hepatitis: implications for phenotypic heterogeneity and biomarkers for drug response. *Hum Genomics*. 2021;15(1):6. doi: 10.1186/s40246–020–00301–4
12. Barliana MI, Afifah NN, Amalia R, et al. Genetic Polymorphisms and the Clinical Response to Systemic Lupus Erythematosus Treatment Towards Personalized Medicine. *Front Pharmacol*. 2022;13:820927. doi: 10.3389/fphar.2022.820927
13. Ceballos FC, Chamizo-Carmona E, Mata-Martín C, et al. Pharmacogenetic Sex-Specific Effects of Methotrexate Response in Patients with Rheumatoid Arthritis. *Pharmaceutics*. 2023;15(6):1661. doi: 10.3390/pharmaceutics15061661
14. Zhang Q, Lin J, Zhang Z, et al. MTHFR Polymorphism and Folic Acid Supplementation Influence Serum Homocysteine Levels in Psoriatic Patients Treated with Methotrexate. *J Clin Med*. 2022;11(15):4580. doi: 10.3390/jcm11154580
15. Zhu J, Wang Z, Tao L, et al. MTHFR Gene Polymorphism Association With Psoriatic Arthritis Risk and the Efficacy and Hepatotoxicity of Methotrexate in Psoriasis. *Front Med (Lausanne)*. 2022;9:869912. doi: 10.3389/fmed.2022.869912
16. Fedota O, Roschenyuk L, Tyzhnenko T, et al. Methotrexate effect on biochemical indices of psoriasis patients depends on MTHFR gene polymorphism. *Ukr Biochem J*. 2020;92(1):66-74. doi: 10.15407/ubj92.01.066
17. Fedota O, Roschenyuk L, Tyzhnenko T, et al. Pharmacogenetic effects of methotrexate (mtx) in ukrainian patients depending on the mthfr genotypes (clinical cases). *Georgian Med News*. 2018;279:111-117.
18. Ni G, Qin J, Li H, et al. Effects of antiepileptic drug monotherapy on one–carbon metabolism and DNA methylation in patients with epilepsy. *PLoS One*. 2015;10(4):e0125656. doi: 10.1371/journal.pone.0125656

19. Hwang Y, Yun HJ, Jeong JW, et al. Co-inhibition of glutaminolysis and one–carbon metabolism promotes ROS accumulation leading to enhancement of chemotherapeutic efficacy in anaplastic thyroid cancer. *Cell Death Dis*. 2023;14(8):515. doi: 10.1038/s41419–023–06041–2
20. George AK, Majumder A, Ice H, et al. 2020. Genes and genetics in hyperhomocysteinemia and the "1–carbon metabolism": implications for retinal structure and eye functions. *Can J Physiol Pharmacol*. 2020;98(2):51-60. doi: 10.1139/cjpp–2019–0236
21. van Vliet MM, Schoenmakers S, Gribnau J, et al. The one–carbon metabolism as an underlying pathway for placental DNA methylation – a systematic review. *Epigenetics*. 2024;19(1):2318516. doi: 10.1080/15592294.2024. 2318516
22. Steluti J, Carvalho AM, Carioca AAF, et al. Genetic Variants Involved in One–Carbon Metabolism: Polymorphism Frequencies and Differences in Homocysteine Concentrations in the Folic Acid Fortification Era. *Nutrients*. 2017;9(6):539. doi: 10.3390/nu9060539
23. Tinelli C, Di Pino A, Ficulle E, et al. Hyperhomocysteinemia as a Risk Factor and Potential Nutraceutical Target for Certain Pathologies. *Front Nutr*. 2019;6:49. doi: 10.3389/fnut.2019.00049
24. McCaddon A, Miller JW. Homocysteine–a retrospective and prospective appraisal. *Front Nutr*. 2023;10:1179807. doi: 10.3389/fnut.2023.1179807
25. Ducker GS, Rabinowitz JD. One–Carbon Metabolism in Health and Disease. *Cell Metab*. 2017;25(1):27-42. doi: 10.1016/j.cmet.2016.08.009
26. Huang X, Li D, Zhao Q, et al. Association between BHMT and CBS gene promoter methylation with the efficacy of folic acid therapy in patients with hyperhomocysteinemia. *J Hum Genet*. 2019;64(12):1227-1235. doi: 10.1038/s10038–019–0672–7
27. Arumugam MK, Paal MC, Donohue TM Jr, et al. Beneficial Effects of Betaine: A Comprehensive Review. *Biology (Basel)*. 2021;10(6):456. doi: 10.3390/biology10060456
28. Fedota O, Puzik N, Skrypkina I, et al. Single nucleotide polymorphism C994g of the cytochrome P450 gene possess pleiotropic eff ects in Bos taurus, L. *Acta Biologica Szegediensis*. 2022;66(1):7-15. doi: 10.14232/abs.2022.1.7–15
29. Pascale RM, Simile MM, Calvisi DF, et al. S–Adenosylmethionine: From the Discovery of Its Inhibition of Tumorigenesis to Its Use as a Therapeutic Agent. *Cells*. 2022;11(3):409. doi: 10.3390/cells11030409
30. Lee SY, Ko KS. Effects of S-Adenosylmethionine and Its Combinations With Taurine and/or Betaine on Glutathione Homeostasis in Ethanol–induced Acute Hepatotoxicity. *J Cancer Prev*. 2016;21(3):164-172. doi: 10.15430/JCP.2016.21.3.164
31. Lee SY, Ko KS. Protective Effects of S-Adenosylmethionine and Its Combinations With Taurine and/or Betaine Against Lipopolysaccharide or Polyinosinic–polycytidylic Acid-induced Acute Hepatotoxicity. *J Cancer Prev*. 2016;21(3):152-163. doi: 10.15430/JCP.2016.21.3.152
32. Freedman BL, Danford CJ, Patwardhan V, et al. Treatment of Overlap Syndromes in Autoimmune Liver Disease: A Systematic Review and Meta–Analysis. *J Clin Med*. 2020;9(5):1449. doi: 10.3390/jcm9051449
33. Zhang H, Yang J, Zhu R, et al. Combination therapy of ursodeoxycholic acid and budesonide for PBC–AIH overlap syndrome: a meta–analysis. *Drug Des Devel Ther*. 2015;9:567-74. doi: 10.2147/DDDT.S74515
34. Leuschner M, Maier KP, Schlichting J, et al. Oral budesonide and ursodeoxycholic acid for treatment of primary biliary cirrhosis: results of a prospective double–blind trial. *Gastroenterology*. 1999;117(4):918-925. doi: 10.1016/s0016–5085(99)70351–3
35. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of liver diseases in pregnancy. *J Hepatol*. 2023;79(3):768-828. doi: 10.1016/j.jhep.2023.03.006
36. Hernandez S, Hindorff LA, Morales J, et al. Patterns of pharmacogenetic variation in nine biogeographic groups. *Clin Transl Sci*. 2024;17(9):e70017. doi: 10.1111/cts.70017
37. Koturbash I, Yeager RP, Mitchell CA, et al. Botanical–induced toxicity: Liver injury and botanical–drug interactions. A report on a society of Toxicology Annual Meeting symposium. *Regul Toxicol Pharmacol*. 2024;153:105708. doi: 10.1016/j.yrtph.2024.105708
38. Unified clinical protocol of primary, secondary (specialized), medical aid. Autoimmune hepatitis]. Kyiv: Publishing House "KIM"; 2014:40.
39. Mack CL, Adams D, Assis N, et al. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. *Hepatology*. 2020;72(2):671-722. doi: 10.1002/hep.31065
40. Fedota O, Sadovnychenko I, Chorna L, et al. The Effects of Polymorphisms in One–carbon Metabolism Genes on Manifestation of Ichthyosis Vulgaris. *Open Access Maced J Med Sci*. 2021;9(A):291–7. doi: 10.3889/oamjms.2021.6004
41. Lee KR, Gulnaz A, Chae YJ. Drug Interaction–Informed Approaches to Inflammatory Bowel Disease Management. *Pharmaceutics*. 2024;16(11):1431. doi: 10.3390/pharmaceutics16111431
42. Moore CD, Roberts JK, Orton CR, et al. Metabolic pathways of inhaled glucocorticoids by the CYP3A enzymes. *Drug Metab Dispos*. 2013;41(2):379-389. doi: 10.1124/dmd.112.046318
43. Kilanczyk E, Banales JM, Wunsch E, et al. S–adenosyl–L–methionine (SAMe) halts the autoimmune response in patients with primary biliary cholangitis (PBC) via antioxidant and S–glutathionylation processes in cholangiocytes. *Biochim Biophys Acta Mol Basis Dis*. 2020;1866(11):165895. doi: 10.1016/j.bbadis.2020.165895
44. Arumugam MK, Paal MC, Donohue TM Jr, et al. Beneficial Effects of Betaine: A Comprehensive Review. *Biology (Basel)*. 2021;10(6):456. doi: 10.3390/biology10060456

45. Lawson–Yuen A, Levy HL. The use of betaine in the treatment of elevated homocysteine. *Mol Genet Metab*. 2006;88(3):201-207. doi: 10.1016/j.ymgme.2006.02.004
46. Maclean KN, Jiang H, Greiner LS, et al. Long-term betaine therapy in a murine model of cystathionine beta–synthase deficient homocystinuria: decreased efficacy over time reveals a significant threshold effect between elevated homocysteine and thrombotic risk. *Mol Genet Metab*. 2012;105(3):395-403. doi: 10.1016/j.ymgme.2011.11.190
47. Fedota O, Babalian V, Ryndenko V, et al. Lactose tolerance and risk of multifactorial diseases on the example of gastrointestinal tract and bone tissue pathologies. *Georgian Med News*. 2020;(303):109-113.
48. Kalola UK, Ambati Sh. *Budesonide*. In: StatPearls. Treasure Island (FL): StatPearls https://www.ncbi.nlm.nih.gov/books/NBK563201. Accessed August 28, 2023.
49. Pratt VM, Cavallari LH, Fulmer ML, et al. CYP3A4 and CYP3A5 Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, and Pharmacogenomics Knowledgebase. *J Mol Diagn*. 2023;25(9):619-629. doi: 10.1016/j.jmoldx.2023.06.008
50. Dorofieieva V, Borysenko T, Fedota O. Diagnosis of liver cirrhosis on the background of mutations H63D of the *HFE* gene and H1069Q of the *ATP7B* gene associated with Hemochromatosis and Wilson's Disease (Clinical Case). *Ukr J Med Biol Sports*. 2022;3(37):120-126. doi: 10.26693/jmbs07.03.120
51. Bessone F, Hernandez N, Mendizabal M, et al. Serious liver injury induced by Nimesulide: an international collaborative study. *Arch Toxicol*. 2021;95(4):1475-1487. doi: 10.1007/s00204–021–03000–8
52. Pomey MP, Schaad B, Lasserre–Moutet A, et al. Towards a New Integrated Model for Taking Into Account the Experiential Knowledge of People With Chronic Diseases, Integrating Mediation, Therapeutic Education and Partnership: The Expanded Chronic Care Patient–Professional Partnership Model. *Health Expect*. 2024;27(5):e70054. doi: 10.1111/hex.70054