World Journal of Hepatology

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DOI: 10.4254/wjh.v7.i29.2920

World J Hepatol 2015 December 18; 7(29): 2920-2926
ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

PAI-1 4G-4G and MTHFR 677TT in non-hepatitis C virus/ hepatitis B virus-related liver cirrhosis

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Author contributions: Pasta L designed and performed the research, analyzed the data and wrote the paper; Pasta F performed the research, analyzed the data and wrote the paper.

Institutional review board statement: The local human research committee of AOOR of Palermo approved this retrospective study.

Informed consent statement: All participants gave their informed consent prior to their inclusion in the study, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Conflict-of-interest statement: All the authors declare that they have no competing interests.

Data sharing statement: The technical appendix, statistical code and dataset are available from the corresponding author at: lindpas@yahoo.it.

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Received: May 29, 2015
Peer-review started: June 2, 2015
First decision: August 22, 2015
Revised: September 4, 2015
Accepted: November 23, 2015
Article in press: November 25, 2015

Published online: December 18, 2015

Abstract

AIM: To evaluate the different roles of thrombophilia in patients with and without viral etiology. The thrombophilic genetic factors (THRGFs), PAI-1 4G-4G, MTHFR 677TT, V Leiden 506Q and prothrombin 20210A, were studied as risk factors in 1079 patients with liver cirrhosis (LC), enrolled from January 2000 to January 2014.

METHODS: All Caucasian LC patients consecutively observed in a fourteen-year period were included; the presence of portal vein thrombosis (PVT) and Budd Chiari syndrome (BCS) was registered. The differences between the proportions of each THRGF with regard to the presence or absence of viral etiology and the frequencies of the THRGF genotypes with those predicted in a population by the Hardy-Weinberg equilibrium were registered.

RESULTS: Four hundred and seventeen/one thousand and seventy-six patients (38.6%) showed thrombophilia: 217 PAI-1 4G-4G, 176 MTHFR C677TT, 71 V Leiden factor and 41 prothrombin G20210 A, 84 with more than 1 THRGF; 350 presented with no viral liver cirrhosis (NVLC) and 729 with, called viral liver cirrhosis (VLC), of whom 56 patients were hepatitis C virus + hepatitis B virus. PAI-1 4G-4G, MTHFR C677TT, the presence of at least one TRHGF and the presence of > 1 THRGF, were statistically more frequent in patients with NVLC *vs* patients with VLC: All $\chi^2 > 3.85$ and $P < 0.05$. Patients with PVT and/or BCS with at least one TRHGF were 189/352 (53.7%). The Hardy-Weinberg of PAI-1 and MTHFR 677 genotypes deviated from that expected from a population in equilibrium in patients with NVLC (respectively $\chi^2 = 39.3$; $P < 0.000$ and $\chi^2 = 27.94$; $P < 0.05$), whereas the equilibrium was respected in VLC.

CONCLUSION: MTHFR 677TT was nearly twofold and PAI-1 4G-4G more than threefold more frequently found in NVLC *vs* patients with VLC; the Hardy-Weinberg equilibrium of these two polymorphisms confirms this data in NVLC. We suggest that PAI-1 4G-4G and MTHFR 677TT could be considered as factors of fibrosis and thrombosis mechanisms, increasing the inflammation response, and causing the hepatic fibrosis and augmented intrahepatic vascular resistance typical of LC. PAI-1 4G-4G and MTHFR 677TT screening of LC patients could be useful, mainly in those with NVLC, to identify patients in which new drug therapies based on the attenuation of the hepatic stellate cells activation or other mechanisms could be more easily evaluated.

Key words: PAI-1 4G-4G; MTHFR 677TT; V Leiden 506Q; Prothrombin 20210A; Liver cirrhosis; Portal vein thrombosis; Budd Chiari syndrome; Fibrogenesis

Core tip: This study on thrombophilia in 1079 patients with liver cirrhosis showed that PAI-1 4G-4G and MTHFR C677TT were statistically more frequent in 350 patients with no viral liver cirrhosis *vs* 729 patients with viral liver cirrhosis. In the same patients, PAI-1 and MTHFR 677 genotypes deviated from that expected from a population in the Hardy-Weinberg equilibrium. PAI-1 4G-4G and MTHFR 677TT could be considered as factors increasing the inflammation response mechanisms, causing fibrogenesis and augmented intrahepatic vascular resistance, typical of liver cirrhosis. New drug therapies based on the attenuation of these mechanisms could be very easily evaluated in these patients.

Pasta L, Pasta F. PAI-1 4G-4G and MTHFR 677TT in non-hepatitis C virus/hepatitis B virus-related liver cirrhosis. *World J Hepatol* 2015; 7(29): 2920-2926 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i29/2920.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i29.2920

INTRODUCTION

We studied the thrombophilic genetic factors (THRGFs), PAI-1 4G-4G, MTHFR 677TT, V Leiden 506Q and prothrombin 20210A, as risk factors in patients with liver cirrhosis (LC). We have published two studies on the prevalence of these THRGFs in LC. The first study included 214 patients with LC, enrolled from January 2000 to December 2007[1]. In this study, we demonstrated the significant role of PAI-1 4G-4G, MTHFR C677TT and prothrombin G20210A in patients with hepatocellular carcinoma (HCC) *vs* healthy controls, but we did not analyze the role of THRGF in patients with LC. The second study included 865 patients from June 2008 to January 2014[2]. In this study, we demonstrated the pivotal role of PAI-1 4G-4G and MTHFR 677TT in patients with alcoholic and cryptogenic LC and provided the hypothesis that thrombo and fibro-genetic mechanisms of PAI-1 4G-4G and MTHFR 677TT could have a role in the development of LC, mainly in patients without hepatitis C virus (HCV) and hepatitis B virus (HBV) etiology.

To evaluate the different role of thrombophilia, in patients with and without viral etiology, we analyzed the total number of patients with LC recruited by our group by asking the question if these THRGFs could be potential markers of liver fibrogenesis, mainly in patients without viral etiology.

We built a file with data of the individual patients with LC from the two studies described above from 2000 to 2014[1,2] and compared the results of the analysis with those from the literature that support the hypothesis of a pathogenetic role of thrombophilia in liver fibrogenesis.

MATERIALS AND METHODS

Patients

The first study included 214 patients with LC, enrolled from January 2000 to December 2007[1], and the second, 865 patients from June 2008 to January 2014[2].

Inclusion criteria: All Caucasian patients with a diagnosis of LC consecutively observed in the Medicine and Liver Department of the Emergency Hospital of Palermo were included. Exclusion criteria: Non-Caucasian patients or those with biliary cirrhosis, autoimmune cirrhosis, celiac disease, HCC and other neoplasms were excluded. The presence of portal vein thrombosis (PVT) and the extension of the thrombosis to the mesenteric or splenic vein was registered and accepted when unambiguous diagnostic evidence was detected by proper imaging techniques. All patients underwent endoscopy and the size of esophageal varices was recorded as large-medium/small-absent. All patients were asked if they had a history of episodes of gastrointestinal bleeding. The local human research committee approved this study protocol.

We analyzed the data of patients with regard to the various etiologies and the patients were also analyzed separately in two subgroups: The first with virus C and/or B and the second with alcoholic and cryptogenic cirrhosis, as our second study showed that only the latter patients showed a significant frequency of THRGFs.

THRGFs and definition of thrombophilia

To evaluate the role of PAI-1, MTHFR677, V Leiden 506Q and prothrombin 20210A mutations, genotyping of these polymorphisms was performed by PCR-RFLP, according to Patnaik *et al*[3], in both heterozygous and homozygous statuses. We defined genetic thrombophilia as the presence of at least one of the following THRGFs: PAI-1 4G-4G, MTHFR 677TT, V Leiden Q506 and prothrombin 20210A, as in our previous studies[1,2]. All patients signed an informed consent form and the study conformed to the ethical guidelines of the 1975 Helsinki

Table 1 Main demographic and clinical characteristics of patients with hepatitis C/B virus liver cirrhosis, defined virus liver cirrhosis and alcoholic and cryptogenic, aggregated as non-virus cirrhosis

	Total (%)	VLC (%)	Alcoholic (%)	Crypto (%)	NVLC (%)
Patients	1079 (100)	729 (100)	102 (100)	248 (100)	350 (100)
Age (range)	57 (19-83)	60 (24-83)	55 (19-80)	49 (19-83)	51 (19-83)
Male sex	620 (57.5)	384 (52.7)	81 (79.4)	155 (62.5)	236 (67.4)
PVT/BCS	352 (32.6)	230 (31.5)	45 (44.1)	77 (31.0)	122 (34.8)
MVT/SVT	53 (4.9)	33 (4.5)	6 (5.8)	14 (5.6)	20 (5.7)
L-M varices	445 (41.2)	574 (78.7)	48 (47.0)	150 (60.4)	245 (70.0)
N° bleeding	360 (33.3)	265 (36.3)	41 (40.1)	54 (21.7)	95 (27.1)
Child A/B/C	416/242/430	241/194/294	31/53/17	129/31/83	165/48/17
	(38.5/22.4/39.8)	(33.0/26.6/40.3)	(30.3/51.9/16.6)	(52.0/12.5/33.4)	(47.1/13.7/39.1)

No statistical differences between VLC *vs* NVLC group: All $\chi^2 > 3.85$ and $P < 0.05$. VLC: Virus liver cirrhosis; NVLC: Non-virus cirrhosis; PVT: Portal vein thrombosis; BCS: Budd Chiari syndrome; MVT: Mesenteric vein thrombosis; SVT: Splenic vein thrombosis.

Table 2 Frequencies of thrombophilic genetic factors, PAI-1 4G-4G, MTHFR 677TT, V Leiden 506Q and prothrombin 20210A, in patients with hepatitis C/B virus liver cirrhosis, alcoholic and cryptogenic, aggregated as non-virus cirrhosis

	(A) VLC (%)	Alcoholic (%)	Crypto (%)	(B) NVLC (%)	(A) *vs* (B) χ^2: *P* value; OR (95%CI)
Patients	729 (100)	102 (100)	248 (100)	350 (100)	-
PAI-1 4G-4G	95 (13.0)	33 (32.3)	89 (35.8)	122 (34.8)	68.2: 0.000; 3.6 (2.6-4.9)
MTHFR 677TT	99 (13.5)	14 (13.7)	63 (25.4)	77 (22.0)	11.7: 0.001; 1.8 (1.3-2.5)
V Leiden 506Q	41 (5.6)	9 (8.8)	22 (8.8)	30 (8.6)	3.3: 0.09; 1.5 (0.9-2.6)
Prothrombin 20210A	25 (3.4)	3 (2.9)	13 (5.2)	16 (4.5)	0.8: 0.39; 1.4 (0.7-2.7)
At least 1 THRGF	218 (29.9)	43 (42.1)	156 (62.9)	199 (56.9)	72.5: 0.000; 3.1 (2.4-4.1)
> 1 THRGF	40 (5.4)	14 (13.7)	30 (12.0)	44 (12.5)	16.5: 0.000; 2.5 (1.6-4.0)

VLC: Virus liver cirrhosis; NVLC: Non-virus cirrhosis; THRGF: Thrombophilic genetic factors.

Declaration.

Statistical analysis

We looked at the differences between the proportions of each THRGF, with regard to the presence or absence of viral etiology, using the contingency tables[4]. We only considered statistically significant differences, if the $\chi^2 > 3.84$ and P value < 0.05.

Moreover, we compared the observed frequencies of the THRGF genotypes with those predicted in a population by the Hardy-Weinberg equilibrium using a web interactive calculator[5].

RESULTS

The whole group consisted of 1079 patients: 336 patients showed PVT and 16 Budd Chiari syndrome; 53 patients showed mesenteric and/or splenic vein thrombosis associated with PVT; large-medium esophageal varices were present in 445 patients and 360 patients had had at least one gastrointestinal bleeding episode.

The main demographic and clinical characteristics of patients, declared in the previous original studies[1,2], are synthesized in Table 1. The patients were separated into two subgroups: The first with alcoholic and cryptogenic cirrhosis, *i.e.*, without viral etiology, (350 patients) called no viral cirrhosis (NVLC), and the second with virus B and/or C (729 of whom 56 patients were HCV + HBV), called viral liver cirrhosis (VLC). No statistical differences were found between NVLC *vs* VLC demographic and clinical characteristics: All $\chi^2 > 3.85$ and $P < 0.05$.

A total of 189/352 patients with PVT and/or BCS showed at least one TRHGF; in 177, PAI-1 4G-4G and/or MTHFR 677TT were present.

Table 2 shows the frequencies of the studied THRGFs in the 1079 patients with cirrhosis of various etiologies and with regard to the presence of virus. A total of 417/1079 patients (38.6%) showed thrombophilia: 217 PAI-1 4G-4G, 176 MTHFR C677TT, 71 V Leiden factor and 41 prothrombin G20210 A, 84 with more than 1 THRGF (82 patients with 2 THRGFs; 2 patients, 3).

Not one V with Leiden 506Q or Prothrombin 20210A homozygous was present. The proportion of PAI-1 polymorphisms 4G-5G and 5G-5G was, respectively, 123 and 121 in NVLC and 354 and 280 in VLC; the proportion of MTHFR polymorphisms C677T and CC677 was, respectively, 161 and 112 in NVLC and 364 and 266 in VLC.

NVLC and VLC showed at least one THRGF in 198/350 and 199/729 patients, respectively.

We tested the statistical differences of the single THRGF between patients with NVLC and VLC, with 2-way contingency table analysis. Table 2 shows the corresponding χ^2, P values and odd ratios with 95% with confidence intervals (OR, with 95%CI). V Leiden factor and prothrombin G20210 did not show statistical

differences. PAI-1 4G-4G, MTHFRC677TT, the presence of thrombophilia and the presence of > 1 THRGF were statistically more frequent in patients with NVLC *vs* patients with VLC: All χ^2 > 3.85 and P < 0.05. A total of 178/350 (50.8%) NVLC *vs* 179/729 (24.5%) VLC showed a significant proportion of PAI-1 4G-4G and/or MTHFRC677TT: χ^2 = 73.8, P value < 0.000, 95%CI: 3.2 (2.4-4.2).

The Hardy-Weinberg of PAI-1 and MTHFR 677 genotypes deviated from that expected from a population in equilibrium in patients with NVLC (respectively χ^2 = 39.3; P < 0.000 and χ^2 = 27.94; P < 0.05 respectively), whereas the equilibrium was respected in VLC. Leiden Q506 and prothrombin 20210A Hardy-Weinberg equilibrium was respected in the two groups of patients.

DISCUSSION

This study was planned to evaluate the proportions of THRGFs, PAI-1 4G-4G, MTHFR 677TT, V Leiden 506Q and prothrombin 20210A, in a large sample of patients with LC, recruited in two prospective studies[1,2]. In the second of these studies, we found that thrombo and fibro-genetic mechanisms of PAI-1 4G-4G and MTHFR 677TT could have a role in the development of LC, mainly in patients without HCV and HBV.

Many authors for many years have studied the intrinsic mechanisms of fibrogenesis in liver diseases with and without associated viruses. In our study, 417/1079 (38.6%) patients with LC showed thrombophilia. We did not find any correlation with factor V Leiden and prothrombin 20210A, even although many authors have found a correlation with hepatic fibrogenesis[6,7]. We mainly focused our attention on the role of PAI-1 4G-4G and MTHFR 677TT. The prevalence of PAI-1 4G-4G in patients with LC was more frequent than that of MTHFR 677TT in our study: 217 and 176. A total of 357/1079 (33.1%) showed the presence of PAI-1 4G-4G and/or MTHFR 677TT, with a significant difference between patients with NVLC *vs* VLC: 178/350 (50.8%) and 179/729 (24.5%).

MTHFR 677TT is nearly twofold and PAI-1 4G-4G over threefold more frequently found in NVLC *vs* patients with VLC, as shown in Table 2. Moreover, the Hardy-Weinberg equilibrium of these two polymorphisms confirms these data in NVLC.

A limitation of this study is the inability to compare our data since no comparable data have been published, mainly for PAI-1 4G-4G. This was a single center study and the patients were all Caucasian, almost exclusively from Sicily; this could lead to a high genetic frequency of these two genes on the basis of the geographical belonging, typical of populations of the islands, as in the case of Wilson's disease in Sardinia[8].

We did not estimate the correlation between the degree of liver fibrosis and the presence of thrombophilia markers; this correlation must be evaluated in future studies, including other factors such as protein C and S deficiency, antithrombin Ⅲ, increased serum levels of factor Ⅷ, resistance to thrombomodulin action, *etc*. In future studies, suitable systems to measure the speed of the portal flow, another risk factor for thrombosis development, should also be developed. Finally, the relationship between the flow velocity and the presence of thrombophilia should be studied.

Regarding PAI-1 4G-4G, there are many studies demonstrating the role of this THRGF associated with the highest serum PAI-1 activity[9] in the liver fibrosis process. PAI-1 has an active role in liver fibrosis in rats[10] through a pathogenic mechanism leading to the hepatic stellate cell (HSC) activation[11]. The relationship between ethanol, liver and PAI-1 in alcoholic liver diseases was very recently reviewed by Liu[12]; alcohol up-regulates PAI-1 and its level can be used as an index for the severity of the disease. Patients with nonalcoholic steatohepatitis showed significantly higher PAI-1 values than those with normal liver, as found by Verrijken *et al*[13]. These observations seem to be sufficient to explain why patients with PAI-1 4G-4G have an increased risk of fibrosis progression to LC development in patients without HCV or HBV.

There are many active drugs for fibrolysis, with the goal of lowering the PAI-1 synthesis. Some models of the action of these drugs on PAI 1 activity are reported below; the final objective of these drugs is the reduction of the activation of HSC caused by PAI-1. Sauchinone blocks the transforming growth factor (TGF)-β1-induced phosphorylation of Smad 2/3, the transcript levels of plasminogen activator inhibitor-1 and matrix metalloproteinase-2, as well as autophagy in HSC[14].

Spironolactone partially reverses the effects of aldosterone that promote HSC activation and the expression of TGF-β1, PAI-1 and collagen in hepatic fibrosis progression partially mediated by TGF-β1, as studied by Wang *et al*[15].

Statins lead to a profound amelioration in HSC phenotype activated by the oxidant and inflammatory pathways and counteract the stimulatory effect of tumor necrosis factor-α on secretion and expression of PAI-1. Other treatments are under evaluation for the treatment of liver fibrosis, as reported by Gracia-Sancho *et al*[16]; the last futuristic treatment is the use of nanoparticles to transport and deliver nitric oxide into the HSC[17].

Regarding MTHFR 677TT and fibrogenesis, there is much evidence that MTHFR 677TT has a role in the progression of liver diseases. Patients with MTHFR 677TT have higher serum total homocysteine, as reported by Devlin *et al*[18]. MTHFR 677TT polymorphism promotes liver fibrosis progression in patients with recurrent hepatitis C[19] and steatosis and fibrosis in patients with chronic hepatitis C[20].

Hyperhomocysteinemia determines damage of endothelial cells, reduces the flexibility of vessels and adversely affects the process of hemostasis. In addition, hyperhomocysteinemia enhances the adverse effects of risk factors such as hypertension, smoking and impaired glucose, lipid and lipoprotein metabolism, as well as

promoting the development of inflammation, as found by Baszczuk *et al*[21]. Hyperhomocysteinemia is highly prevalent in LC but not in other chronic liver diseases, mainly in patients with MTHFR 677TT; it may contribute to fibrogenesis and vascular complications of LC, as reported by Ventura *et al*[22]. The hyperhomocysteinemia causes endothelial dysfunction, as studied by Cheng *et al*[23]. According to this last study, hyperhomocysteinemia causing oxidative stress determines loss of the normal phenotype of liver sinusoidal endothelial cells (LSEC); the consequent cross-talk between LSEC and HSC induces activation of the latter ones, which in turn proliferate, migrate and increase collagen deposition around the sinusoids, contributing to fibrogenesis, architectural disruption and angiogenesis, as reported by Gracia-Sancho *et al*[16].

Regarding the therapy of MTHFR 677TT polymorphism and the consequent increase of serum homocysteine, there are no tested drugs for patients with this polymorphism apart from folic acid therapy. The administration of folic acid in a dose of 15 mg/d obtains a decrease in the concentration of homocysteine in serum, as recently demonstrated in patients with primary arterial hypertension by Baszczuk *et al*[24].

In conclusion, both PAI-1 4G-4G and MTHFR 677TT cause HSC activation, now recognized as the origin of liver fibrogenesis. This imbalance of the PAI-1 4G-4G and MTHFR 677TT allele frequency is possible evidence of the role of these two polymorphisms in the pathogenesis of LC through SHC activation, today considered the key of liver fibrogenesis.

As reported very recently by Trautwein *et al*[25], it is necessary to accelerate progress in understanding mechanisms of hepatic fibrosis and defining therapeutic targets in order to establish clinical trial designs that can accurately assess the efficacy of antifibrotic drugs.

For these reasons, we think it is important to find patients at the greatest risk for disease progression to ensure that these risk factors can be balanced between placebo and control groups in randomized controlled trials. In our study, PAI-1 4G-4G and MTHFR 677TT were present in up to 50% of patients with NVLC; we think that these genetic factors could be reliably used to stratify risk in clinical trials of new drugs aimed at obtaining the reduction of fibrosis or increase of fibrolysis, also to be evaluated in patients with HBV and/or HCV infection.

We think that drugs that cause the lowering of HSC activation could be better tested in patients with genetic markers such as PAI-1 4G-4G and MTHFR 677TT. These patients could be the tip of the iceberg in a population that produces fibrosis in the liver as well as in other organs (heart, lung, kidney and skin), as reported by Ghosh *et al*[26] with regards to PAI-1 and by Reilly *et al*[27] with regards to MTHFR 677TT.

We suggest that PAI-1 4G-4G and MTHFR 677TT may increase the inflammation response, participating in the activation of HSC and causing hepatic fibrosis and augmented intrahepatic vascular resistance in cirrhosis, as suggested by Fernandez[28]. These two genetic markers share the ultimate goal of increasing the activation of HSC, directly or by the action of LSEC on HSC.

We hope that all relevant studies can suggest new perspectives for developing strategies more effective in lowering fibrosis progression, with the common objective of the attenuation of the HSC activation and consequently liver fibrosis.

In conclusion, PAI-1 4G-4G and MTHFR 677TT could be considered as factors of thrombosis and fibrosis mechanisms that lead to the development of cirrhosis and augmented intrahepatic vascular resistance.

PAI-1 4G-4G and MTHFR 677TT screening of patients could be useful, mainly in those with alcoholic or cryptogenic cirrhosis, to identify patients in which new drug therapies based on the attenuation of the HSC activation or other mechanisms could be more easily evaluated.

The recent articles by Lee *et al*[29] and Gracia-Sancho *et al*[16] deal with the new drugs in the attempt to develop new strategies of combined therapies directed towards multi-targeted different pathophysiological mechanisms (*i.e.*, microvascular dysfunction/angiogenesis or fibrosis/microvascular dysfunction); the goal of new therapies includes efforts to inhibit fibrogenesis and promote resolution of fibrosis. The evaluation of the genetic profile of thrombophilia (obviously as complete as possible) of patients with chronic liver diseases could be considered a noninvasive method to assess the dynamics of fibrogenesis and fibrolysis on a genetic basis.

As an immediate clinical application of the results of our study according to the principles of the translational medicine[29], we think it is advisable to screen patients with chronic liver disease for a genetic predisposition to liver fibrogenesis, as well as in patients with hepatic virus diseases, where these genetic markers can lead to a lower response to the antiviral drugs.

In conclusion, it could be recommended that a complete analysis of the risk of progression of liver fibrosis should include all thrombophilia factors.

In patients with MTHFR 677TT, folic acid supplementation should be prescribed. Patients with PAI-1 4G-4G and perhaps MTHFR 677TT represent a subset of patients in which trials of statins, anti-aldosterone, antioxidants and other drugs should be tested to obtain more rapid results, although none of these drugs are approved yet. Combination therapies should include their association with antiviral treatment and non-selective beta-blockers. In patients with portal vein thrombosis, severe portal hypertension or deep vein thrombosis, thromboprophylaxis with low molecular weight heparins should be recommended, according to Rodriguez-Castro *et al*[30].

COMMENTS

Background

In this study, 417/1079 (38.6%) patients with liver cirrhosis (LC) showed

thrombophilia and PAI-1 4G-4G and MTHFR C677TT were statistically more frequent in 350 patients with no viral LC *vs* 729 patients with viral LC. In the same patients, PAI-1 and MTHFR 677 genotypes deviated from that expected from a population in the Hardy-Weinberg equilibrium.

Research frontiers

Many authors for many years have studied the intrinsic mechanisms of fibrogenesis in liver diseases with and without associated viruses. They suggest that PAI-1 4G-4G and MTHFR 677TT could be considered as factors of fibrosis and thrombosis mechanisms, increasing the inflammation response and causing the hepatic fibrosis and augmented intrahepatic vascular resistance typical of LC.

Innovations and breakthroughs

PAI-1 4G-4G and MTHFR 677TT could be considered as factors increasing the response inflammation mechanisms, causing fibrogenesis and augmented intrahepatic vascular resistance typical of LC.

Applications

PAI-1 4G-4G and MTHFR 677TT screening of hepatic chronic liver disease patients could be useful, mainly in those with no virus-related diseases, to identify patients in which new drug therapies based on the attenuation of the hepatic stellate cell activation or other mechanisms could be evaluated more easily.

Terminology

Genetic thrombophilia is involved in fibrosis and thrombosis mechanisms, increasing the inflammation response and causing the hepatic fibrosis and augmented intrahepatic vascular resistance typical of chronic liver diseases. In this study, the authors defined genetic thrombophilia as the presence of at least one of the following thrombophilic genetic factors: PAI-1 4G-4G, MTHFR 677TT, V Leiden Q506 and prothrombin 20210A.

Peer-review

There are many studies demonstrating the role of PAI-1 4G-4G associated with the highest serum PAI-1 activity in the liver fibrosis process. Regarding MTHFR 677TT and fibrogenesis, patients with MTHFR 677TT had a higher serum total homocysteine and there is much evidence that MTHFR 677TT has a role in the progression of fibrosis in liver diseases.

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