

# Heterozygous $\alpha_1$ -antitrypsin deficiency in liver transplant candidates

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## KEY WORDS

$\alpha_1$ -antitrypsin deficiency, liver cirrhosis, liver diseases

## ABSTRACT

**INTRODUCTION** It is estimated that in about 1% of all liver transplant candidates liver cirrhosis is caused by hereditary homozygous  $\alpha_1$ -antitrypsin (AAT) deficiency.

**OBJECTIVES** The aim of the study was to evaluate the role of heterozygous AAT deficiency in the development of liver cirrhosis leading to liver transplantation.

**PATIENTS AND METHODS** In the years 2009–2011, we conducted a prospective study of 304 consecutive patients (men, 57%) scheduled for orthotopic liver transplantation. AAT phenotyping and the clinical assessment of hepatic and cardiopulmonary functions were performed in all subjects.

**RESULTS** The most common causes of liver cirrhosis were viral hepatitis (21%) and alcohol abuse (12%). Normal protease inhibitor (Pi) MM phenotype was observed in 284 patients. The PiMZ phenotype was detected in 11 subjects (4%), which indicates its higher prevalence in patients with liver cirrhosis compared with the general population (2%). PiMS phenotype was found in 6 patients (2%), and this value was similar to that observed in the Polish population. In 3 patients, less common phenotypes were observed: MP, IM, and MX.

**CONCLUSIONS** The PiMZ phenotype may be an independent risk factor for the development of liver cirrhosis along with the most common causes, namely, viral hepatitis and alcohol abuse.

**INTRODUCTION**  $\alpha_1$ -antitrypsin (AAT) deficiency, a hereditary disease described by Laurell and Eriksson,<sup>1</sup> affects around 1 million homozygotic subjects and 116 million carriers worldwide.<sup>2</sup> This genetic disorder may manifest clinically as pulmonary emphysema, liver cirrhosis, and necrotizing panniculitis.<sup>3</sup> AAT is a serine protease inhibitor synthesized predominantly in the liver and targeting mainly neutrophil elastase. Deficient alleles are responsible for abnormal folding and polymerization of AAT inside the hepatic cell which prevents its secretion to the bloodstream.<sup>4</sup> Severe AAT deficiency results in the reduction of circulating AAT and may lead to the development of pulmonary emphysema caused by lung protease-antiprotease imbalance and uninhibited proteolytic attack on elastic lung fibers.<sup>3</sup>

Liver injury in severe AAT deficiency results from the degradation of protein accumulated in the hepatocyte. Close to 10% of infants with protease inhibitor (Pi) ZZ phenotype in a large Swedish cohort presented clinical manifestations of liver disease.<sup>5</sup> Further follow-up of this cohort showed that at the age of 26 years, only 9% of PiZZ subjects demonstrated marginal elevation of liver enzymes.<sup>6</sup> However, at autopsy, one-third of 35 AAT-deficient subjects presented the signs of liver cirrhosis.<sup>7</sup> Leading to a variety of structural changes and end-stage organ failure, homozygotic AAT deficiency is a well-recognized underlying condition in the field of lung and liver transplantation, but plays no role in the transplantation of other organs.<sup>4,8,9</sup>

Data on the prevalence of AAT deficiency in patients with severe liver disease are unequivocal.

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Received: October 18, 2012.

Revision accepted: December 7, 2012.

Published online: December 11, 2012.

Conflict of interest: none declared.

Pol Arch Med Wewn. 2013;

123 (1-2): 14-20

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Some authors suggest that carriers of a single AAT deficiency allele are more frequently found in adults with severe liver disease than in the general population.<sup>10,11</sup> Others did not confirm such an association.<sup>12,13</sup> The nature of liver disease that may be associated with AAT deficiency generates controversy.<sup>10,11</sup> It seems that the clinical presentation may range from neonatal cholestasis to cirrhosis and hepatocellular carcinoma.<sup>14</sup> Although generally a deficient PiZ allele has been found in patients with liver disease, single cases of PiMS phenotype have also been reported.<sup>11</sup> Age also seems to play an important role in clinical presentation of heterozygous AAT deficiency in patients with liver disease, with more pronounced symptoms in older age groups.<sup>15</sup> Of note, studies on relative contribution of congenital and environmental factors in the pathogenesis of liver diseases have not been limited to the SERPINA 1 gene. Other genetic predispositions that might be involved in liver injury due to infectious or toxic agents have also been evaluated. These include mutations of human hemochromatosis protein gene in patients with alcoholic liver disease.<sup>16</sup>

The aim of the present study was to evaluate AAT phenotype in a large, nonselected group of adult patients with chronic liver disease considered for liver transplantation and to investigate the relationship between the frequency of mutant AAT alleles and the type of liver disease.

**PATIENTS AND METHODS** This prospective study was conducted in a referral center for liver transplantation where over 1000 liver transplantations had been performed. A total of 304 consecutive patients with chronic liver disease scheduled for orthotopic liver transplantation between 2009 and 2011 were enrolled. The study protocol was approved by the Bioethics Committee of the Medical University of Warsaw and all patients had signed written informed consent.

The medical history was obtained from each patient, including demographics, signs and symptoms, information concerning alcohol consumption and potential abuse, risk factors for viral liver diseases, inherited disorders, as well as medication and toxin exposure. All patients underwent physical examination and a series of diagnostic tests designed to determine the etiology of liver disorder. Appropriate biochemical tests were performed to assess liver function and prognosis using various scoring systems, i.e., Child-Pugh classification and the Model for End-stage Liver Disease.<sup>17,18</sup>

Chest X-rays, echocardiography, pulmonary function tests (PFTs), and arterial blood gas (ABG) analysis were performed for cardiopulmonary evaluation. The PFTs included spirometry (Lungtest 1000, MES, Poland), body plethysmography with lung volumes, airway resistance, and lung diffusion capacity for carbon monoxide ( $DL_{CO}$ ) (Vmax Series 229/V6200, Sensor Medics Corporation, Yorba Linda, United States).

Depending on the nature of liver disease, patients were classified into 2 groups: 1) with disease leading to liver cirrhosis, and 2) with liver disease without cirrhosis. Patients were further subclassified according to a specific liver disease.

**$\alpha_1$ -antitrypsin concentration and phenotyping assessment** Plasma AAT concentration was measured in all subjects by the turbidimetric method (expected normal range, 90–200 mg/dl). AAT phenotyping of the serine protease inhibitor was performed by isoelectric focusing as previously described.<sup>19</sup>

**Statistical analysis** A statistical analysis was performed using a statistical software package (STATISTICA, ver. 9.0, StatSoft Inc., United States). Data are presented as mean  $\pm$  standard deviation when the data were normally distributed and median (interquartile range) when the data were not normally distributed. The Shapiro-Wilk *W* test was used to assess normal distribution for all variables. For variables inconsistent with normal distribution, we used the corresponding nonparametric tests (Mann-Whitney test or Wilcoxon signed-rank test for nonrelated and related samples, respectively). A *P* value below 0.05 was considered statistically significant.

**RESULTS** The study group consisted of 172 men (57%) and 132 women. There were 285 subjects (94%) with cirrhotic and 19 subjects (6%) with noncirrhotic liver diseases. The distribution of different liver diseases in cirrhotic and noncirrhotic groups is shown in **TABLE 1**.

The mean age of patients was 46.3  $\pm$  12.9 years (range, 18–69 years). Patients were divided according to the Child-Pugh classification: class A included 138 subjects, class B – 123, and class C – 42. Demographic data and data on liver disease scoring are presented in **TABLE 2**. Sixty-five patients (21%) were active smokers, while 97 (79%) were ex-smokers. The results of PFTs and data on tobacco-smoke exposure are presented in **TABLE 3**.

The mean serum concentration of AAT in the studied patients was normal: 183.6  $\pm$  47.6 mg/dl. There were only 7 patients with reduced plasma AAT concentration, and 1 patient had elevated AAT concentration.

**$\alpha_1$ -antitrypsin phenotyping** Complete diagnostic testing including AAT phenotyping was performed in all patients. There were 284 patients with the MM phenotype (93%), 11 patients (4%) with the MZ phenotype, and 6 patients (2%) with the MS phenotype. Three heterozygotes presenting rare phenotypes, namely, MP, IM, and MX, were also identified.

**Characteristics of patients with MZ phenotype** Demographic data, characteristics of liver disease, and serum AAT concentration in patients with the MZ phenotype are shown in **TABLE 4**. All 11 patients had cirrhotic liver disease. Sex

**TABLE 1** Distribution of different liver diseases in cirrhotic and noncirrhotic groups

Underlying liver disease	Number of patients (%)
<b>cirrhotic liver diseases</b>	<b>285 (94)</b>
alcoholic	36 (12)
HCV	50 (16.5)
HBV	14 (4.5)
AIH	15 (4.5)
PBC	17 (5.5)
PSC	32 (10.5)
toxic other than alcoholic	4 (1.5)
Wilson's disease	3 (1)
combined	45 (15)
Budd-Chiari syndrome	2 (0.5)
cryptogenic	19 (6.5)
iatrogenic	4 (1.5)
biliary cysts	1 (0.3)
cystic fibrosis	3 (1)
sarcoidosis	1 (0.3)
tumor in cirrhotic liver	39 (13)
<b>noncirrhotic liver diseases</b>	<b>19 (6)</b>
tumor in healthy liver	10 (3)
echinococcus	5 (1.5)
polycystic liver disease	4 (1.5)

Abbreviations: AIH – autoimmune hepatitis, HBV – hepatitis B virus, HCV – hepatitis C virus, PBC – primary biliary cirrhosis, PSC – primary sclerosing cholangitis

**TABLE 2** Demographic characteristics and liver disease scoring of the study group

Variable	Median (IQR)
age, y	50.0 (36.0–56.0)
BMI, kg/m <sup>2</sup>	23.6 (21.0–28.0)
duration of liver disease, mo	36.0 (12.0–96.0)
duration of liver cirrhosis, mo	24.0 (7.0–60.0)
Child-Pugh classification, points	7.0 (6.0–8.0)
MELD classification, points	11.9 (8.7–15.7)

Abbreviations: BMI – body mass index, IQR – interquartile range, MELD – model for end-stage liver disease

**TABLE 3** Smoking history and pulmonary function tests in the study group

Variable	Median (IQR)
pack-years (in current and former smokers)	18.5 (8.0–30.0)
FEV <sub>1</sub> % pred.	102.0 (85.0–113.0)
FVC% pred.	104.0 (91.0–116.0)
FEV <sub>1</sub> %/FVC	80.0 (75.0–83.0)
RV% pred.	112.0 (94.0–124.0)
DL <sub>CO</sub> % pred.	64.0 (51.0–74.0)

Abbreviations: DL<sub>CO</sub> – lung diffusion capacity for carbon monoxide, FEV<sub>1</sub> – forced expiratory volume in 1 second, FVC – forced volume capacity, RV – residual volume, others – see **TABLE 2**

distribution was even. Two patients were classified as Child-Pugh class A, 7 as class B, and 2 as class C. Most patients in this group had viral hepatitis and alcoholic cirrhosis. In 5 of 11 patients, the plasma AAT concentration was below the normal value with the average of 45%

predicted. The results of PFTs and ABG in this patient group are presented in **TABLE 5**.

The only patient referred due to suspected liver disease secondary to AAT deficiency was a 29-year-old men with the serum AAT of 59.0 mg/dl. However, as the second measurement showed the serum AAT concentration of 96 mg/dl and phenotyping revealed the PiMZ phenotype, he was classified as PiMZ heterozygote. This was confirmed in a genotype analysis (Sanger sequencing), which revealed E342K mutation in a heterozygous form. The results of PFTs in this patient were within the normal range.

**Characteristics of patients with MS phenotype** Demographic data, characteristics of liver disease, and serum AAT concentration in patients with the MS phenotype are shown in **TABLE 6**. There were 5 patients with cirrhotic liver disease (83%). Sex distribution was even. Three patients were classified as Child-Pugh class A and 3 as class B. In all patients with the MS phenotype, the plasma AAT concentration was within the normal range. The results of PFTs and ABG are presented in **TABLE 5**.

**Comparison of heterozygotic groups** There were no differences in sex, age, body mass index, history of smoking, and scores in the Child-Pugh classification between both heterozygotic groups (**TABLE 7**). The plasma AAT concentration was significantly lower in the group with the MZ phenotype compared with the group with the MS phenotype.

**DISCUSSION** We conducted a prospective study on the prevalence of AAT deficiency in a large, nonselected group of patients scheduled for orthotopic liver transplantation. The study was performed in Poland, a country with a genetically homogenous population.<sup>20</sup>

Of all subjects, 6% were carriers of a single AAT allele, 4% presented with PiZ, and 2% with PiS allele. The prevalence of a deficient PiZ allele was significantly higher in our study group than in the general Polish population, in which the prevalence of PiZ heterozygotes is 1.05%. The prevalence of the PiS allele was similar to that in the general population (1.75%).<sup>21</sup>

Our results are in line with the previously published data. Graziadei et al.<sup>10</sup> performed AAT phenotyping in 599 adults prior to orthotopic liver transplantation. The PiMZ phenotype was found in 8.2% of the patients, which was significantly higher than reported in the American population studies (2%–4%). All PiMZ patients had liver cirrhosis. The prevalence of the PiMS phenotype in our study population did not differ from that observed in the general population. Interestingly, 14 patients in the Graziadei group were transplanted for end-stage liver disease related to homozygous PiZZ deficiency.

Hodges et al.<sup>11</sup> performed AAT phenotyping in 1055 liver biopsy specimens from patients with liver cirrhosis or chronic active hepatitis.

**TABLE 4** Characteristics of 11 patients with the MZ phenotype

Patient initials	Age, y	Sex	$\alpha_1$ -antitrypsin, mg/dl	Etiology of liver disease	Cirrhosis	Duration of symptomatic illness, mo	Child-Pugh class
P.K.	41	male	189	alcoholic	yes	6	B
P.M.	62	male	183	HBV + tumor	yes	240	A
G.M.	53	female	210	cryptogenic	yes	18	B
I.P.	58	female	152	HBV + PBC	yes	348	B
T.T.	54	male	60	HCV	yes	84	C
M.B.	49	female	73	HCV	yes	24	B
B.B.	29	male	96	cryptogenic	yes	24	A
S.B.	59	male	143	alcoholic + tumor	yes	60	B
E.K.	53	female	84	HCV	yes	144	C
W.N.	53	female	93	alcoholic	yes	120	B
R.Z.	48	male	103	cryptogenic	yes	20	B

Abbreviations: see [TABLE 1](#)**TABLE 5** Selected results of pulmonary function tests and arterial blood gases in patients with PiMZ and PiMS phenotypes

Patient initials / phenotyping	FEV <sub>1</sub> , l % pred.	FEV <sub>1</sub> /FVC%	TLC, l % pred.	RV, l % pred.	DL <sub>CO</sub> , ml/min/mmHg % pred.	PaO <sub>2</sub> , mmHg	P(A-a)O <sub>2</sub> , mmHg
P.K./MZ	3.75 (99)	77.0	7.84 (116)	2.34 (122)	17.4 (55)	82.3	29.5
P.M./MZ	2.21 (70)	70.0	5.30 (79)	2.12 (89)	15.5 (57)	65.4	38.5
G.M./MZ	3.15 (120)	79.0	6.24 (121)	2.24 (121)	18.2 (74)	99.6	11.0
I.P./MZ	2.15 (90)	75.7	NA	NA	NA	80.6	28.7
T.T./MZ	2.04 (55)	83.0	4.76 (65)	2.20 (94)	11.2 (36)	69.4	47.6
M.B./MZ	3.01 (125)	81.0	5.82 (126)	2.06 (126)	12.3 (53)	92.3	12.3
B.B./MZ	4.34 (107)	86.0	6.61 (99)	1.58 (94)	27.1 (82)	99.7	NA
S.B./MZ	3.42 (107)	79.0	6.24 (94)	1.83 (79)	NA	78.3	34.4
E.K./MZ	2.85 (123)	85.0	5.25 (113)	1.90 (111)	NA	88.3	23.9
W.N./MZ	2.95 (107)	85.0	5.75 (107)	2.28 (119)	NA	79.3	30.1
R.Z./MZ	3.98 (104)	77.0	7.45 (102)	2.26 (102)	NA	106.0	8.3
G.B./MS	2.66 (142)	85.0	5.31 (116)	2.18 (112)	16.0 (80)	83.4	23.3
Z.R./MS	2.29 (86)	75.0	5.78 (110)	2.75 (146)	13.4 (54)	99.3	12.9
E.W./MS	3.85 (129)	80.0	6.82 (105)	1.89 (79)	21.9 (84)	86.8	15.5
U.S./MS	2.24 (71)	86.0	4.28 (79)	1.58 (94)	NA	71.5	35.1
R.U./MS	4.05 (94)	87.0	6.75 (92)	2.09 (114)	NA	99.7	15.0
A.Z./MS	4.03 (93)	84.0	6.48 (93)	1.62 (99)	NA	103.0	0.0

Abbreviations: NA – not available, PaO<sub>2</sub> – partial pressure of oxygen in the blood, P(A-a)O<sub>2</sub> – alveolar-arterial gradient, TLC – total lung capacity, others – see [TABLE 3](#)**TABLE 6** Characteristics of 6 patients with the MS phenotype

Patient initials	Age, y	Sex	$\alpha_1$ -antitrypsin, mg/dl	Etiology of liver disease	Cirrhosis	Duration of symptomatic illness, mo	Child-Pugh class
G.B.	69	female	249	echinococcus	no	24	A
Z.R.	54	female	99	cryptogenic	yes	1	B
E.W.	63	male	127	HCV + tumor	yes	96	A
U.S.	38	female	214	alcoholic	yes	7	B
R.U.	31	male	254	PSC	yes	12	B
A.Z.	18	male	280	PSC + AIH	no	2	A

Abbreviations: see [TABLE 1](#)

**TABLE 7** Comparison of selected variables in both heterozygotic groups

Variable	MZ phenotype (n = 11)	MS phenotype (n = 6)	P
age, y	53.0 (48.0–58.0)	46.0 (31.0–63.0)	NS
BMI, kg/m <sup>2</sup>	25.6 (23.0–28.4)	19.9 (19.0–23.1)	NS
Child-Pugh classification, points	8.0 (7.0–9.0)	6.5 (6.0–8.0)	NS
smoking history, pack-years	17.5 (6.5–32.5)	20.0 (10.0–30.0)	NS
$\alpha_1$ -antitrypsin, mg/dl	103.0 (84.0–183.3)	231.3 (127.0–254.0)	<0.05

Data are presented as median (IQR).

Abbreviations: NS – nonsignificant, others – see **TABLE 2**

A significantly higher prevalence of the PiMZ phenotype was observed in subjects with cryptogenic cirrhosis and chronic active hepatitis.

Fischer et al.<sup>22</sup> found a significantly higher rate of PiZ-positive cases in subjects with liver disease than in the reference group of autopsy cases. Similar results were reported by Eigenbrodt et al.<sup>23</sup>

Other authors came to different conclusions.<sup>12,13</sup> Bell et al.<sup>12</sup> observed that none of their 53 patients with autoimmune chronic active hepatitis had the PiMZ phenotype. However, higher incidence of the PiMZ phenotype was demonstrated in patients with cryptogenic or alcoholic cirrhosis. Vennarecci et al.<sup>13</sup> found no association between heterozygosity of the AAT gene and liver disease. To some extent, these discrepancies might be explained by a small number of patients (n = 80) and the use of biopsy material, both affecting the reliability of the calculated prevalence of AAT deficiency.<sup>24</sup>

The vast majority of our patients (93%) presented with potentially cirrhotic liver disease, the most frequent etiological factors being hepatic viral infection, alcohol abuse, and primary sclerosing cholangitis. This finding is in line with the results reported by other authors.<sup>10,11,22,23</sup>

**Heterozygous PiMZ patients** All heterozygous PiMZ patients (n = 11) were diagnosed with cirrhotic liver of alcoholic or viral etiology. Six patients (54.5%) had a long history of their illness (duration of more than 5 years). In 5 patients, the AAT level was low with the average of 45% predicted. Only 1 patient in this group was referred with the diagnosis of AAT deficiency. Child-Pugh class A or B was reported for 9 of 11 patients (82%), and the proportion was similar to that observed in a larger group by Graziadei et al.<sup>10</sup> So far, two of these patients underwent liver transplantation, with an uneventful posttransplant follow-up of 18 and 21 months, respectively. As the number of transplanted PiMZ patients was small and the follow-up in this group was relatively short, we were not able to discuss the results of the long-term follow-up in these patients and compare them with those of PiMM subjects who had undergone liver transplantation.

**Heterozygous PiMS patients** The prevalence of PiMS carriers in our study was similar to that

observed in the general Polish population. Cirrhotic liver disease was diagnosed in 4 of 6 patients. The history of the disease in this patient group was much shorter compared with PiMZ patients. However, the only statistically significant difference between the groups was an abnormally low AAT level in the PiMZ group. Four patients with the PiMS phenotype underwent liver transplantation at the time of the study. Two patients died (at 63 and 338 postoperative days, respectively). The fatal outcomes were not associated with the PiMS phenotype but resulted from early-onset postoperative complications related to severely impaired preoperative health status (both patients) and biliary complications related to underlying primary sclerosing cholangitis (1 patient). Two other patients survived 17 and 29 months, respectively, and no serious complications were noted. As in PiMZ patients, this group was also too small and the follow-up was too short to address the issue of the long-term results of liver transplantation.

Abnormal folding and polymerization of AAT in the liver of homozygous AAT-deficient subjects relatively rarely results in liver failure requiring liver transplantation. AAT deficiency accounts for 1% of all liver transplants in the United States.<sup>25</sup>

There were 31 patients (10%) with obstructive ventilatory impairment in spirometry. However, all patients with PiMZ or PiMS showed normal spirometric values and none of these patients presented with the spirometric pattern typical for emphysema. Although impaired DL<sub>CO</sub> was a common finding in the entire group, this was most probably related to hepatopulmonary syndrome rather than to emphysema. As many as 27.1% of the patients met the criteria for hepatopulmonary syndrome, and the mean DL<sub>CO</sub> value in these patients was significantly lower than in the remaining subjects. Hence, the mean DL<sub>CO</sub> for the entire group was relatively low.

Initially, we speculated that the development of liver cirrhosis in patients with any liver disease (acquired or congenital) and 1 deficient AAT allele (PiZ or PiS) may be more rapid than in patients with the PiMM phenotype. Therefore, we analyzed the time interval between the first diagnosis of liver disease and the diagnosis of liver cirrhosis. We found that in cirrhotic patients with

AAT PiMM phenotype, the time was 36.6 ±61.9 months, while in 15 subjects with liver cirrhosis and 1 deficient AAT allele it was 35.1 ±84.5 months (nonsignificant).

We are aware of several limitations of our study. First, the study group was recruited only in 1 transplantation center and therefore reflects the patient profile characteristic of that center. On the other hand, our institution is the most active liver transplantation center in Poland, performing approximately 38% of all liver transplantations in our country. Thus, patients enrolled to our study had come from different regions of Poland.

Second, our study group was heterogeneous and, contrary to other studies, included not only subjects with liver cirrhosis, but also patients with noncirrhotic liver diseases. Moreover, there was a significant difference in the number of patients between both groups. This is due to the fact that our study was aimed at investigating the prevalence of different AAT phenotypes in nonselected group of patients evaluated as potential candidates for liver transplantation.

Third, the number of patients with the PiMZ and PiMS phenotypes was relatively low. Hence, the assessment of the relationship between the prevalence of mutant AAT alleles and various chronic liver diseases was difficult.

In conclusion, it seems that even heterozygous deficiency of AAT PiMZ type may influence the natural course in a variety of liver diseases. The incidence of heterozygous AAT deficiency in a large, unselected group of patients with liver failure evaluated for liver transplantation was significantly higher than in the general Polish population. A decreased serum AAT level in that group indicates abnormal metabolism of AAT in the liver cells.

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# Heterozygotyczny niedobór $\alpha_1$ -antytrypsyny u pacjentów kwalifikowanych do przeszczepienia wątroby

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## SŁOWA KLUCZOWE

choroby wątroby,  
marskość wątroby,  
niedobór  
 $\alpha_1$ -antytrypsyny

## STRESZCZENIE

**WPROWADZENIE** Ocenia się, że u około 1% chorych na marskość wątroby kwalifikowanych do przeszczepienia tego narządu przyczyną marskości jest wrodzony, homozygotyczny niedobór  $\alpha_1$ -antytrypsyny (AAT).

**CELE** Celem pracy była ocena roli heterozygotycznego niedoboru AAT w rozwoju marskości wątroby prowadzącej do konieczności leczenia przeszczepieniem wątroby.

**PACJENCI I METODY** W latach 2009–2011 przeprowadzono prospektywne badanie 304 kolejnych pacjentów (57% mężczyzn), zakwalifikowanych do leczenia za pomocą ortotopowego przeszczepienia wątroby. U wszystkich chorych wykonano oznaczenie fenotypu genu odpowiedzialnego za syntezę AAT, przeprowadzono kliniczną ocenę funkcji wątroby, układu oddechowego oraz układu sercowo-naczyniowego.

**WYNIKI** Najczęstszą przyczyną marskości wątroby w badanej grupie chorych stanowiły wirusowe zapalenia wątroby (21%) oraz marskość alkoholowa (12%). Prawidłowy fenotyp inhibitora proteazy (*protease inhibitor* – Pi) MM stwierdzono u 284 badanych. Fenotyp PiMZ wykazano u 11 (4%) osób, co wskazuje na jego częstsze występowanie u chorych na marskość wątroby niż w ogólnej populacji (2%). Fenotyp PiMS stwierdzono u 6 (2%) chorych i ta wartość jest podobna do wartości stwierdzanej w populacji ogólnej. U 3 chorych wykryto rzadsze fenotypy: MP, IM, oraz MX.

**WNIOSKI** Obecność fenotypu PiMZ może być niezależną przyczyną rozwoju marskości wątroby obok najczęstszych przyczyn, jakimi są wirusowe choroby zapalne wątroby oraz nadużywanie alkoholu.

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Praca wpłynęła: 18.10.2012.  
Przyjęta do druku: 07.12.2012.  
Publikacja online: 11.12.2012.  
Nie zgłoszono sprzeczności  
interesów.

Pol Arch Med Wewn. 2013;  
123 (1-2): 14-20

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