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primary biliary cholangitis, cholestasis, autoimmune liver diseases, PBC

COMPARATIVE CHARACTERISTICS OF AMA-POSITIVE AND AMA-NEGATIVE PRIMARY BILIARY CHOLANGITIS

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Abstract

Primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis) is one of the most significant diseases that is predominantly verified in women. The prevalence of PBC is 1.9-40.2 per 100,000 population. Antimitochondrial antibodies (AMA) are of major importance for the diagnosis of primary biliary cirrhosis (PBC), and it has also been suggested that they may be involved in the pathogenesis of the disease.

Objective*: The aim of this study was to characterize the clinical, biochemical parameters and response to UDCA (Paris I criteria) PBC patients depending on AMA status in the Republic of Kazakhstan.*

Material and methods*. The study was conducted on the basis of the Research Institute of Cardiology and Internal Diseases from 2014 to 2019. A total of 212 patients with primary biliary cholangitis were recorded.*

Results. *Among 212 patients, 171 (80.7%) were AMA-positive and 41(19,3%) - AMA-negative. Vast majority of patients in both groups were Asian (179; 84.4%) and female (206; 97.2%). Severe disease (F3/4) was revealed in 108 (63.2%) AMA-positive and in 18 (43.9 %) AMA-negative patients (p>0.05). AMA-positive and AMA-negative PBC were associated with autoimmune hepatitis in 88 (51.5%) and 10 (24.4%) cases (p<0.01), rheumatoid arthritis in 26 (15.2%) and 5 (12.2%), autoimmune thyroiditis in 35 (20.5%) and 4 (9.8%), vitamin D deficiency in 89 (52.1%) and 19 (46.3%), osteoporosis in 48(28.1%) and 7 (17.1%), gallstone disease in 43 (25.4%) and 8 (21.2%) respectively (p >0.05). Response to ursodeoxycholic acid (UDCA) treatment according to Paris I criteria was noted in 24 out of 81 (29.6%) AMA-positive and in 9 out of 22 (40.9%) AMA-negative patients (p>0.05).*

Conclusion*. In patients with AMA-positive PBC compared with AMA-negative, there is a statistically significant high value of autoimmune hepatitis and autoimmune thyroiditis. Whereas, response to UDCA treatment according to Paris I criteria is higher in AMA-negative PBC.*

АМА-оң және АМА-теріс біріншілік билиарлы холангиттің салыстырмалы сипаттамасы

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Тұжырым

Біріншілік билиарлы холангит (ПБХ, бұрын біріншілік билиарлы цирроз деп аталған) көбінесе

әйелдерде жиі кездесетін маңызды аурулардың бірі болып табылады. ПБХ таралуы 100000 тұрғынға шаққанда 1,9-40,2 құрайды. Антимитохондриялық антиденелер (АМА) бастапқы билиарлы холангитті (ПБХ) диагностикалауда үлкен маңызға ие және олар аурудың патогенезіне де қатысуы мүмкін деп болжанған.

Мақсаты. *Зерттеудің мақсаты Қазақстан Республикасындағы АМА мәртебесіне байланысты ПБХ науқастарында клиникалық, биохимиялық көрсеткіштерді және терапияға жауапты - УДХК (Париж критерийлері I) сипаттау болды.*

Материал және әдістер. *Зерттеу 2014-2019 жылдар аралығында Кардиология және ішкі аурулар ҒЗИ негізінде жүргізілді.*

Нәтижелер. *212 пациенттің 171-і (80,7%) АМА - позитивті және 41-і (19,3%) ама-теріс болды. Екі топтағы науқастардың басым көпшілігі азиялықтар (179; 84,4%) және әйелдер (206; 97,2%) болды. Ауыр ағым (F3/4) 108 (63,2 %) АМА-оң және 18 (43,9 %) АМА-теріс науқастарда (p>0,05) анықталды. АМА-оң және АМА-теріс ПБХ аутоиммунды гепатитпен 88 (51,5%) және 10 (24,4%) жағдайда (p<0,01), ревматоидты артритпен 26 (15,2% және 5 (12,2%) жағдайда), аутоиммунды тиреоидитпен 35 (20,5%) және 4 (9,8%), Д витаминінің жетіспеушілігі 89 (52,1%) және 19 (46,3%), остеопороз 48 (28,1%) және 7 (17,1%), өт тас ауруы сәйкесінше 43 (25,4%) және 8 (21,2%) (p>0,05). Париж критерийлері бойынша УДХК емдеуге жауап і ама-оң 81-ден 24-те (29,6%) және 22-ден 9-да (40,9%) АМА-теріс пациенттерде (p>0,05) байқалды.*

Қорытынды. *АМА-оң ПБХ-мен салыстырғанда ама-теріс пациенттерде аутоиммунды гепатит пен аутоиммунды тиреоидиттің статистикалық маңызды жоғары мәні бар. Париж I критерийлеріне сәйкес УДХК емдеуге жауап АМА-теріс ПБХ-да жоғары екенін ескере отырып.*

Түйінді сөздер:
біріншілік билиарлы холангит, холестаз, бауырдың аутоиммунды аурулары, ПБХ.

Сравнительная характеристика АМА-позитивного и АМА-негативного первичного билиарного холангита

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Абстракт

Первичный билиарный холангит (ПБХ, ранее известный как первичный билиарный цирроз) является одним из наиболее значимых заболеваний, которое преимущественно верифицируется у женщин. Распространенность ПБХ составляет 1,9- 40,2 на 100 000 населения. Антимитохондриальные антитела (АМА) имеют большое значение для диагностики первичного билиарного холангита (ПБХ), и также предполагалось, что они могут быть вовлечены в патогенез заболевания.

Цель исследования *- охарактеризовать клинические, биохимические показатели и ответ на терапию - УДХК (Парижские критерии I) у больных ПБХ в зависимости от статуса АМА в Республике Казахстан.*

Материал и методы. *Исследование проводилось на базе НИИ кардиологии и внутренних болезней с 2014-2019 гг. Всего было зарегистрировано 212 больных первичным билиарным холангитом. Результаты. Среди 212 пациентов 171 (80,7%) были АМА-позитивными и 41 (19,3%) - АМА-негативными. Подавляющее большинство больных в обеих группах были азиаты (179; 84,4%) и женщинами (206; 97,2%). Тяжелое течение (F3/4) выявлено у 108 (63,2%) АМА-положительных и у 18 (43,9%) АМА-негативных больных (p>0,05). АМА-положительный и АМА-негативный ПБХ были ассоциированы с аутоиммунным гепатитом в 88 (51,5%) и 10 (24,4%) случаях (p<0,01), ревматоидным артритом в 26 (15,2% и 5 (12,2%) случаях), аутоиммунным тиреоидитом в 35 (20,5%) и 4 (9,8%), дефицит витамина D у 89 (52,1%) и 19 (46,3%), остеопороз у 48 (28,1%) и 7 (17,1%), желчнокаменная болезнь у 43 (25,4%) и 8 (21,2%) соответственно (p>0,05). Ответ на лечение УДХК по Парижским критериям I отмечен у 24 из 81 (29,6%) АМА-положительных и у 9 из 22 (40,9%) АМА-отрицательных пациентов (p>0,05).*

Заключение. *У больных с АМА-положительным ПБХ по сравнению с АМА-отрицательным имеет место статистически значимое высокое значение аутоиммунного гепатита и аутоиммунного тиреоидита. Принимая во внимание, что ответ на лечение УДХК в соответствии с критериями Paris I выше у АМА-негативного ПБХ.*

Ключевые слова:
первичный билиарный холангит, холестаз, аутоиммунные заболевания печени, ПБХ.

Introduction

Primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis [1] is one of the most significant diseases that is predominantly verified in women. PBC is included in the group of autoimmune cholestatic liver diseases [2, 3, 4]. The prevalence of PBC is 1.9-40.2 per 100,000 population. The disease predominates in women 95% at the age of 30 to 65 years, although there is evidence of an upward trend in prevalence among men [6, 7]. The etiological factors of PBC are still not fully clarified. The combination of adverse environmental factors and immunogenetic background may presumably play an important role in this disease [8, 9]. There are main criteria for setting up primary biliary cholangitis: an increase in the activity of alkaline phosphatase (AP) in combination with the presence of antimitochondrial antibodies - AMA (AMA M2) in a titer> 1:80.

Antimitochondrial antibodies (AMA) are of major importance for the diagnosis of primary biliary cirrhosis (PBC), and it has also been suggested that they may be involved in the pathogenesis of the disease [12]. However, it has long been recognized that 5% to 10% of patients for whom clinical, histological, and laboratory features are diagnostic for PBC, are AMA-negative [13].

In AMA-negative PBC: the presence of cholestasis (increased activity of alkaline phosphatase and / or gamma-glutamyl transpeptidase-GGTP) in combination with specific immunofluorescence ANA-antinuclear antibodies (nuclear dots, perinuclear rims) or the presence of Anti-sp100, Anti-gp210. Additional criteria include: histological evidence of chronic nonsuppurative destructive cholangitis, elevated IgM levels. The disease is chronic and often progressive, leading to end-stage liver disease, cirrhosis, and associated complications [6, 8, 10]. A diagnostically significant indicator for the diagnosis of PBC is the presence of antimitochondrial antibodies (AMA), which are found in serum in more than 90% of patients; specificity of AMA in PBC exceeds 95% [11]. There is a steady increase in this pathology, which is probably due to improved diagnostic capabilities.

Objective. The aim of this study was to characterize the clinical, biochemical parameters and response to UDCA (Paris I criteria) in PBC patients depending on AMA status in the Republic of Kazakhstan.

Material and methods

The study was conducted on the basis of the Research Institute of Cardiology and Internal Diseases from 2014 to 2019. A total of 212 patients with primary biliary cholangitis were recorded. All patients underwent a standard clinical examination, including functional liver tests, autoantibodies spectrum, abdominal ultrasound, and liver histology. To assess the severity of liver disease, indirect elastography, as well as aspartate-aminotransferase to platelet ratio index (APRI), Fibrosis 4 (FIB4), Index Meyo indices were used. Primary sclerosing cholangitis, cancer and pregnancy were excluded. We also analyzed comorbidities in patients in both groups.

All cases fulfilled the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) practice guidelines for PBC [14].

Results

Among 212 patients, 171 (80.7%) were AMA-positive and 41 (19.3%) – AMA-negative. Vast majority of patients in both groups were Asian (179; 84.4%) and female (206; 97.2%). The average age was 53.0±10.5 years without differences depending on AMA-status. According to the results of the examination, 121 patients (57%) showed biochemical activity, of which 101 (59.1%) - in AMA-positive and 20 (48.8%) - in AMA-negative patients without any statistical difference (p=0.25). In general statistics, patients with AMA-positive PBC showed high values for the severity of the disease, concomitant autoimmune disorders and vitamin D deficiency (Table 1). Severe disease (F3/4) was revealed in 108 (63.2%) AMA-positive and in 18 (43.9 %) AMA-negative patients (p>0.05). AMA-positive and AMA-negative PBC were associated with autoimmune hepatitis in 88 (51.5%) and 10 (24.4%) cases (p<0.01), rheumatoid arthritis in 26 (15.2%) and 5 (12.2%), autoimmune thyroiditis in 35 (20.5%) and 4 (9.8%), vitamin D deficiency in 89 (52.1%) and 19 (46.3%), osteoporosis in 48(28.1%) and 7 (17.1%), gallstone disease in 43 (25.4%) and 8 (21.2%) respectively (p >0.05). Response to UDCA treatment according to Paris I criteria was noted in 24 out of 81 (29.6%) AMA-positive and in 9 out of 22 (40.9%) AMA-negative patients (p >0.05).

Table 1.
Patient characteristics According to AMA status

Features	AMA-positive (n=171)	AMA-negative (n=41)	P-value
Biochemical activities	101 (59.1%)	20 (48.8%)	p=0.25
F3, F4	108 (63.2%)	18 (43.9%)	p>0.05
Autoimmune hepatitis	88 (51.5%)	10 (24.4%)	p<0.01
Rheumatoid arthritis	26 (15.2%)	5 (12.2%)	p>0.05
Autoimmune thyroiditis	35 (20.5%)	4 (9.8%)	p>0.05
Vitamin D deficiency	89 (52.1%)	19 (46.3%)	p>0.05
Osteoporosis	48(28.1%)	7 (17.1%)	p>0.05
Gallstone disease	43 (25.4%)	8 (21.2%)	p>0.05

Discussion

Primary biliary cirrhosis is one of the organ-specific autoimmune diseases characterized by the destruction of the biliary epithelial cells, cholestasis, and liver cirrhosis. AMA is a main point of PBC and 84–97% of patients with PBC had AMA [15, 16].

AMA gives reaction against different antigens in the mitochondria. Number of PBC patients has lack of AMA, and these patients are often referred to as AMA-negative PBC. But AMA does not have absolute specificity. [17]. The diagnosis of PBC should be made according to the AASLD guidelines for PBC [18], it is a combination of serological, biochemical and histological examination. In the present study, 19.3% (n=41) PBC patients tested negative for AMA by the use of indirect immunofluorescence, enzyme-linked immunosorbent assay and immunoblotting. This data is in agreement with reports in the literature, indicating that 5–10% of patients with clinical and pathological features of PBC do not have detectable AMA. Our study also detected anti-gp210 and anti-sp100 antibodies in these cases, and these antibodies were positive in some AMA-negative PBC patients, which might be a useful supplementary for the diagnosis. Therefore, we considered that AMA-negative PBC was not 'true' negative but an atypical PBC in which AMA could not be detected by currently available techniques. Antimitochondrial antibody negative PBC patients have similar clinical courses as AMA-positive ones. However, they differ from AMA-positive PBC patients with AMA-negative a higher titre of ANA [19]. Our result also showed that there were no significant differences in clinical characteristics between AMA-negative and -positive PBC patients. Many autoimmune disorders could be associated with PBC, and AMA could be detected in these autoimmune conditions [20].

Conclusion

Summarizing the obtained results, we came to the conclusion that in patients with AMA- positive PBC compared with AMA-negative, there is a statistically significant high value of autoimmune hepatitis and autoimmune thyroiditis. Whereas, response to UDCA treatment according to Paris I criteria is higher in AMA-negative PBC. AMA positive and AMA-negative PBC did not have any statistical differences in terms of age, gender, ethnicity, biochemical profile, and disease severity. Nevertheless, the autoimmune profile of patients with AMA positive and AMA negative PBC needs further study.

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