Measurement of Alpha-fetoprotein Levels in Patients with Chronic Hepatopathy

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ORIGINAL ARTICLE

Abstract

Introduction: Alpha-fetoprotein (AFP) is a glycoprotein associated with hepatic regeneration, as well as with neoplastic processes such as hepatocellular carcinoma (HCC). Nowadays, AFP is used as a criterion for HCC diagnosis, although it is not very sensitive and specific. Objective: The objective of this study was to evaluate the levels of AFP in patients with chronic hepatopathy. Materials and Methods: Patients with chronic hepatopathy and AFP were studied (January 2015-December 2017), including 160 patients. They were classified by etiology (primary biliary cholangitis, HCC, non-alcoholic steatohepatitis, autoimmune hepatitis, alcoholic hepatitis, hepatitis B, hepatitis C, and liver disease of an indeterminate origin). Results: A significant difference was observed between the group of patients with HCC and the other study groups, presenting AFP levels above the reference limit. The other groups showed normal values. Conclusion: Patients with HCC showed high levels of AFP, but not patients with the other hepatopathies studied.

Key words: Alpha-fetoprotein. Hepatocellular carcinoma. Chronic hepatopathy.

Introduction

Alpha-fetoprotein (AFP) is a glycoprotein encoded by one of the genes of the albuminoïd family (which, among others, includes albumin and the Vitamin D binding protein), located on the long arm of chromosome 4. AFP has a molecular weight of 69 kDa and is made up of three domains that give it a shape that resembles a “U.”1

This protein was discovered in 1956 by Bergstrand and Czar using electrophoretic techniques, demonstrating that it migrates between albumin and globulins and that it is expressed mainly during the embryonic period.2 It can be detected after the 1st month of pregnancy, being produced in the yolk sac and later in the liver. In addition, small amounts of AFP are synthesized in the gastrointestinal tract.3 It is produced in minimal quantities in an adult human, due to the strong methylation of its gene.4 Its limited production is carried out by the oval liver cells that surround the bile ducts.1 In adult populations under 40 years of age, a normal AFP value of < 12 ng/mL has been reported.5,6

In 1963, Abelev et al. demonstrated the production of AFP in mice with hepatoma, this being the starting point for further study as a tumor marker.7 Several reports in humans have shown that AFP increases during liver regeneration, especially after resection and massive hepatic necrosis.8 Likewise, its production has been widely described as associated with neoplastic processes such as hepatocellular carcinoma (HCC).9 It

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Medicina Universitaria. 2018;20(4):152-155
www.medicinauniversitaria.org

DOI: 10.24875/RMU.18000018

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has also been reported that AFP levels rise during the onset of chronic hepatopathies such as hepatitis C virus (HCV), hepatitis B virus (HBV), and hepatic cirrhosis without HCC and alcoholic hepatitis (AH)\textsuperscript{10,11}, autoimmune hepatitis (AIH)\textsuperscript{12}, and primary biliary cholangitis (PBC)\textsuperscript{13,14}. The correlation of AFP and hepatic steatosis has not been defined, having been reported that AFP by itself is not an adequate marker to predict the development of steatosis\textsuperscript{15}.

Due to the relationship between AFP values and the presence of various diseases, it is important to know the elevation pattern of this marker in the most common hepatopathies. The objective of this study is to evaluate the levels of AFP in patients with chronic hepatopathy.

**Materials and methods**

A descriptive and retrospective study was carried out in patients of the Hepatology Center of the “Dr. José E. González” University Hospital of the Universidad Autónoma de Nuevo León. This study included patients with chronic hepatopathy and AFP determination from January 2015 to December 2017, considering the most recent value available in their file. AFP reference interval was considered to be between 0.89 and 8.78 ng/mL, according to the chemiluminescent microparticle immunoassay methodology used to measure this marker\textsuperscript{16}. The present investigation was approved by the Ethics and Institutional Research Committee with the number HI18-00001.

The patients were distributed according to their etiology in PBC, HCC, of origin to be determined (OOBD), non-alcoholic steatohepatitis (NASH), AIH, HBV, HCV, and AH. AFP levels of each etiology were compared to establish a statistical difference using an analysis of variance followed by the Tukey test for multiple comparisons using the Prism software (v. 6.0; GraphPad, San Diego, CA, USA). The results were expressed as a mean ± standard deviation and a value of \( p < 0.05 \) was considered a statistically significant difference between the means analyzed.

**Results**

The study included 160 patients. The characteristics of the population and its distribution by etiology are presented in table 1. The group of patients with HCC presented a concentration of 1819.00 ± 3070.00 ng/mL is higher than the AFP reference interval, while the other groups of patients with different hepatopathies showed levels within this range. The levels of AFP in the group with HCC were higher than in the other study groups (PBC, OOBD, NASH, AIH, HBV, HCV, and AH, \( p < 0.001 \)). No significant difference in AFP levels was found between the CBP, OOBD, NASH, AIH, HBV, HCV, and AH groups. AFP values in the distribution of patients according to hepatic etiology are shown in figure 1.

**Discussion**

AFP has been one of the most widely described biomarkers for the diagnosis of HCC, especially in patients

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<th>Table 1. Distribution of the studied population</th>
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<td><strong>Variable</strong></td>
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<td>Age (years) ± SD</td>
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PBC: primary biliary cholangitis; HCC: hepatocellular carcinoma; OOBD: of origin to be determined; NASH: non-alcoholic steatohepatitis; AIH: autoimmune hepatitis; AH: alcohol hepatitis; HBV: hepatitis B virus; HCV: hepatitis C virus.

*HCC versus study group, \( p < 0.001 \).

Figure 1. Alpha-fetoprotein levels according to chronic liver disease. PBC - primary biliary cholangitis; HCC - hepatocellular carcinoma; OOBD - of origin to be determined; NASH - non-alcoholic steatohepatitis; AIH - autoimmune hepatitis; AH - alcohol hepatitis; HBV - hepatitis B virus; HCV - hepatitis C virus.
with chronic hepatopathy\textsuperscript{17,18}. However, despite the association between AFP and HCC, its real utility has been questioned because, by itself, it is considered a marker with variable sensitivity and specificity for HCC\textsuperscript{19,21}. The observed variability is due to the values determined by the technique used, the characteristics of the population, and the level of cutoff used\textsuperscript{22,23}. On the other hand, it has been reported that it is secreted up to 70% of patients with HCC, and according to various clinical guidelines, a value of > 200 ng/mL has been considered diagnostic criteria\textsuperscript{9}. In addition, its usefulness for the prognosis of HCC treatment has been researched\textsuperscript{10}. Sharma et al. demonstrated that AFP ratio/total tumor volume could predict the recurrence of HCC after surgical resection, with a value > 20 indicating a poor prognosis\textsuperscript{24}. Similarly, it was shown that a serum AFP value of < 15 ng/mL implied a significantly higher survival rate than that of patients with a higher AFP value\textsuperscript{25}. In the present study, levels higher than the reference interval (> 200 ng/mL) were observed in all the patients in the HCC group, which agrees with the reports that refer to it as a useful serum tumor marker for the diagnosis of HCC\textsuperscript{26,27}. It has been described that the production of AFP is associated with a process of hepatocyte regeneration after an inflammatory process in diseases of a viral etiology\textsuperscript{28}. Therefore, it has been reported as elevated (> 700 ng/mL) in HBV cases\textsuperscript{29}. In the same way, a correlation between the concentration of AFP and the degree of necrosis and inflammation caused by HCV has been demonstrated. The increase in AFP concentration is not determined by viral load but by the magnitude of tissue damage\textsuperscript{30}. It has been reported that between 10% and 43% of patients with HCV show high levels of AFP\textsuperscript{13,31,32}. In the present study, the population of patients with HBV and HCV showed levels of AFP within the reference range established in this Hepatology Center, which differs with the aforementioned investigations. It has been suggested that high values of AFP by themselves are mainly related to characteristic patterns of tissue damage in non-viral etiologies with AIH and AH. In a cohort of patients with AIH, an increase of AFP was reported while discarding the presence of HCC. However, this elevation was only observed in the acute phase of the disease\textsuperscript{12}. In other studies, an increase in AFP was observed in patients with AH in the acute liver damage stage at the beginning of the disease and then a decrease in the following stages to cirrhosis\textsuperscript{10,11}. In the present study, the groups of patients with AIH, AH, PBC, and NASH showed AFP levels within the reference interval, which agrees with the reported studies, where there was no increase of AFP in the chronic stages.

**Conclusion**

Only the group of patients with HCC showed high levels of AFP, and the groups of patients with other hepatopathies had AFP levels within the reference range established in this Hepatology Center. In this study, it was observed that AFP serum continues to be a useful laboratory test to establish the absence or presence of HCC in various hepatopathies.

**Conflicts of interest**

The authors declare no conflicts of interest.

**Financing**

This project was financed entirely by own resources.

**Ethical disclosures**

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

**References**