APRI as an indicator of advanced liver fibrosis in children with α_1-antitrypsin deficiency

Przydatność APRI w ocenie zaawansowanego włóknienia wątroby u dzieci z niedoborem α_1-antytrypsyny

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Słowa kluczowe: niedobór α_1-antytrypsyny, APRI, włóknienie wątroby, dzieci.

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Abstract

Introduction: Liver biopsy is regarded as a gold standard in assessment of liver fibrosis in children with α_1-antitrypsin deficiency (ATD). Liver fibrosis due to viral infections and alcoholic liver disease can also be assessed by a non-invasive marker – APRI (AST-to-platelet ratio index). As prognosis and progression of liver disease in ATD are variable, non-invasive evaluation of liver fibrosis would be helpful.

Aim: To evaluate APRI as an indicator of advanced liver fibrosis in children with PiZZ phenotype of ATD.

Material and methods: Liver biopsy was performed in 45 patients aged 0.25 years (0.17-0.67 years), median (Q1-Q3). In all subjects APRI and liver histology were analyzed and compared. Liver fibrosis was assessed according to a 5-point scoring system (0-4). Points 2-4 were regarded as advanced fibrosis. Liver cirrhosis was also described. The best sensitivity and specificity of APRI were calculated based on receiver operating characteristic (ROC) analysis and area under curve (AUROC) was assessed.

Results: In the studied group APRI was 0.22 (0.12-0.39), median (Q1-Q3). In 21 children advanced fibrosis was recognized and in 6 patients liver cirrhosis was described. The optimal cut-off value for APRI for advanced fibrosis was 0.26, and for cirrhosis 0.33. Respectively for advanced fibrosis and cirrhosis, sensitivity was 0.60 (95% CI: 0.41-0.77), 0.83 (0.36-0.99); specificity was 0.87 (95% CI: 0.60-0.98), 0.31 (0.17-0.48); AUROC was 0.74 (95% CI: 0.58-0.89), 0.51 (95% CI: 0.28-0.74).

Conclusions: AST-to-platelet ratio index appears to be a sensitive but less specific indicator of cirrhosis in ATD and a valuable marker of advanced liver fibrosis.

Streszczenie

Wstęp: Biopsja wątroby jest złotym standardem w ocenie włóknienia wątroby. Jako nieinwazyjny marker włóknienia u pacjentów z uszkodzeniem wątroby na tle wirusowego zapalenia wątroby typu C, B i alkoholizmu stosuje się APRI (*AST-to-platelet ratio index*). Przebieg choroby i rokowanie u dzieci z niedoborem α_1-antytrypsyny (α_1-*antitrypsin deficiency* – α_1-ATD) są trudne do przewidzenia, dlatego nieinwazyjny wskaźnik zaawansowanego włóknienia byłby przydatny w diagnostyce choroby.

Cel: Ocena przydatności APRI jako wskaźnika zaawansowanego włóknienia wątroby u dzieci z α_1-ATD.

Materiał i metody: Do badania zakwalifikowano 45 dzieci z postacią homozygotyczną α_1-ATD (PiZZ), u których retrospektywnie analizowano APRI w odniesieniu do nasilenia włóknienia wątroby. Biopsję wątroby wykonano u dzieci w wieku średnio 0,25 roku (zakres wieku: 0,17–0,67 roku), mediana (Q1–Q3). Nasilenie włóknienia szacowano w 5-stopniowej skali 0–4. Za zaawansowane uznano włóknienie 2–4, a za marskość 4. Metodą analizy krzywych ROC (*receiver operating characteristic*) i pola pod krzywą ROC (AUROC) stwierdzono własności różnicujące APRI w ocenie zaawansowanego włóknienia wątroby, w tym marskości.

Wyniki: W badanej grupie pacjentów APRI wynosił 0,22 (0,12–0,39), mediana (Q1–Q3). U 21 dzieci rozpoznano zaawansowane włóknienie w biopsji wątroby, natomiast u 6 pacjentów – marskość tego narządu. Optymalny punkt odcięcia dla APRI w odniesieniu do zaawansowanego włóknienia określono na 0,26, a w odniesieniu do marskości – na 0,33. Odpowiednio czułość wynosiła 0,60 (95% CI: 0,41–0,77) i 0,83 (0,36–0,99), swoistość: 0,87 (95% CI: 0,60–0,98) i 0,31 (0,17–0,48), AUROC: 0,74 (95% CI: 0,58–0,89) i 0,51 (95% CI: 0,28–0,74).

Wnioski: APRI jest czułym, ale mało swoistym wskaźnikiem marskości wątroby u dzieci z α_1-ATD i wartościowym, nieinwazyjnym wskaźnikiem zaawansowanego włóknienia wątroby.

Introduction

The major causes of liver fibrosis in adults are chronic hepatitis B and C, and alcoholic (ALD) and non-alcoholic fatty liver disease (NAFLD). About 20-40% of patients with chronic viral hepatitis develop advanced fibrosis and cirrhosis [1, 2].

The risk of end-stage liver disease in ALD increases with cumulative alcohol intake but only a minority of heavy drinkers suffer from advanced disease of the liver [3]. Non-alcoholic fatty liver disease seems to be a growing problem in industrialized countries [4]. The progress of fibrosis in hepatitis B and C is similar, higher in ALD, and the highest in HIV/HCV coinfection. The variable course of these diseases requires systematic follow-up to detect progression to liver cirrhosis.

Liver fibrosis is also often seen in patients with α_1-antitrypsin deficiency (ATD), as early as at the age of 1 year. In the literature it is found to be an indicator of bad prognosis in this group of patients.

Liver biopsy is regarded as the standard of reference for assessment of hepatic fibrosis of various origin. There are some limitations of this procedure: it is invasive, expensive and prone to sampling errors. Elastography (Fibroscan) is a new method that may be useful for the evaluation of liver fibrosis but is limited because of high costs and limited experience in children with various liver diseases.

There is a need to search for a noninvasive, cheap marker to give accurate information about liver fibrosis. Various serum markers have been proposed, but APRI (AST-to-platelet ratio index) [5] and fibrotest (combines total bilirubin, γGT, haptoglobin, apolipoprotein A_1, α_2-macroglobulin, age and gender) are the most validated in various etiologies.

APRI is easily available and low cost. It has been validated in hepatitis B [5] and C [6] and HIV/HCV [7]. It was assessed in NAFLD [8]. APRI appears to be of no value in patients with autoimmune hepatitis. There are not enough data available concerning APRI in liver fibrosis caused by ATD. As prognosis and progression of liver disease in ATD are variable, non-invasive evaluation of liver fibrosis would be helpful to make further diagnostic decisions.

Aim

The aim of the study was to evaluate APRI as an indicator of advanced liver fibrosis in children with PiZZ phenotype of ATD.

Material and methods

We studied 45 children (13 girls) homozygous for ATD (PiZZ), admitted to the Department of Gastroenterology, Hepatology and Eating Disorders, The Children's Memorial Health Institute in Warsaw because of cholestasis or chronic hepatitis from infancy or early childhood. In all subjects APRI and liver histology were analyzed and compared.

All the patients had a platelet count performed on the same day as the biopsy. Aspartate aminotransferase (AST) was assessed within a week before or after the biopsy.

Liver biopsy was performed at the age of 0.25 years (0.17-0.67 years), median (Q_1-Q_3). All biopsies were reviewed by two independent pathologists. Liver fibrosis was assessed according to a 5-point scoring system (0-4). Advanced liver fibrosis was defined as a score ≥ 2. Liver cirrhosis was also described. APRI was applied according to the following formula:

$$\text{APRI} = [(\text{AST level/ULN})/\text{platelet count } (10^9/\text{l})] \times 100,$$

where ULN – upper limit of norm.

The best sensitivity and specificity of APRI were calculated based on receiver operating characteristic analysis and area under curve (AUROC) with StatsDirect Statistical Software http://www.statsdirect.com/Default.aspx.

Results

In the group of 45 patients advanced fibrosis was recognized in 30 children. In 6 out of 45 patients liver cirrhosis was described. In 7 patients there was no fibrosis on liver biopsy. There was a good concordance of findings between two pathologists. In our patients APRI was 0.41 (0.22-0.70), median (Q1-Q3). The optimal cut-off value for APRI for advanced fibrosis was 0.48, and for cirrhosis 0.25. Respectively for advanced fibrosis and cirrhosis, sensitivity was 0.60 (95% CI: 0.41-0.77) and 0.83 (0.36-0.99); specificity was 0.87 (95% CI: 0.60-0.98) and 0.36 (0.21-0.53). The area under the curve of the receiver operator characteristics of the calculated APRI (AUROC) was 0.74 (95% CI: 0.58-0.89) and 0.51 (95% CI: 0.28-0.74) (Table I, Figure 1).

Discussion

In our study of children with ATD APRI appears to be a good marker of liver fibrosis as indicated by relatively high AUROC of 0.74. Only 60% (sensitivity: 0.6) of our patients with advanced fibrosis may be distinguished using the APRI index, so it cannot be used as the only marker to select such a group. On the other hand, 9 out of 10 patients (specificity: 0.87) with an APRI result above the cut-off point of 0.48 have advanced liver fibrosis, so the APRI index may be helpful to indicate particular patients with increased risk of liver disease pro-

Table I. Main features of APRI for advanced fibrosis and cirrhosis in 45 children with ATD
Tabela I. *Główne parametry oceny APRI jako wskaźnika zaawansowanego włóknienia i marskości u 45 dzieci z ATD*

Parameter	Advanced fibrosis	Cirrhosis
Sensitivity (95% CI)	0.6 (0.41-0.77)	0.83 (0.36-0.99)
Specificity (95% CI)	0.87 (0.6-0.98)	0.36 (0.21-0.53)
Cut-off value	0.48	0.25
AUROC	0.74	0.51

gression and requiring more attentive monitoring. But clinical usefulness of APRI in liver cirrhosis detection (AUROC: 0.51) in α_1-ATD in children is doubtful.

Up to now, histopathological assessment of a liver biopsy sample is the most accurate procedure to evaluate liver architecture, stage of chronic processes or to perform differential diagnosis in the case of unrecognized liver disease. Despite invasiveness and limitations it still remains the best method to assess the stage of liver fibrosis. Various indexes of fibrosis based on noninvasive or pictorial (Fibroscan) examinations were estimated in adults with various liver diseases and APRI and Fibrotest among others are currently recommended to be performed before liver biopsy in these patients [9].

The usefulness of APRI as a noninvasive index of liver fibrosis was confirmed in patients with chronic liver damage due to HBV [5], HCV [6], and HIV/HCV [7]. There are very limited data concerning the pediatric population. It was found that APRI but not aspartate to alanine aminotrasferase ratio (AAR), γ-glutamyltransferase to platelet ratio index (GAPRI) and hyaluronic acid/prothrombin index (HAPRI) significantly correlated with the stage of liver fibrosis established by biopsy [10].

De Ledinghen *et al*. compared efficacy of APRI, Fibroscan and Fibrotest to detect liver cirrhosis in children with liver diseases of various etiology. Fibroscan was the most effective but all three methods significantly correlated with liver fibrosis stage. There are no available data concerning APRI effectiveness in liver fibrosis due to ATD. Therefore our results were compared to those obtained in groups of patients with liver fibrosis of other etiology (hepatitis B and C).

Similar values of AUROC (0.69-0.88) were reported in patients with hepatitis C [11-13] whereas they exceed 0.8 in patients with hepatitis B [14].

The sensitivity of APRI for advanced liver fibrosis varies between 41% and 91% and specificity 47% and 95% in adult patients with hepatitis C, which is comparable to our results in children with ATD [11-13].

The sensitivity of APRI for HCV cirrhosis varies between 38.4% and 65.8% and specificity 86.7% and 93%

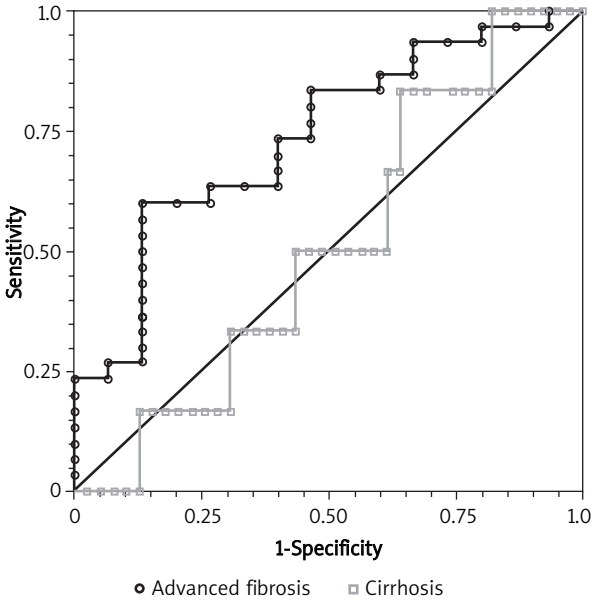

Fig. 1. Receiver-operating characteristic analysis for APRI for advanced fibrosis and cirrhosis in children with ATD
Ryc. 1. *Krzywa ROC dla oceny APRI jako wskaźnika zaawansowanego włóknienia i marskości wątroby u dzieci z ATD*

[13, 15]. We obtained in our group higher sensitivity but much lower specificity.

APRI seems to be doubtful in liver fibrosis assessment in patients with non-alcoholic steatosis. Also in autoimmune hepatitis APRI does not reflect the stage of liver fibrosis, probably due to portal, periportal and lobular inflammation notorious in all stages of fibrosis, which can result in non-differentially high AST levels and, in turn, high APRI values irrespective of fibrosis stage [8, 16, 17].

The value of our study is a relatively large (for this rare disease) group of patients with histopathological findings. Moreover, the patients presented with variable fibrosis that allows comparisons. Still, the study has some significant limitations which cannot be easily overcome in single center studies. We enrolled a small number of patients with cirrhosis (6/45; 13%), which may explain the unsatisfactory results of APRI for detection of cirrhosis. Moreover, liver biopsies were available only at one time point in early life. This is the reason why we cannot indicate the direct prognostic value of APRI. Furthermore, coexistence of hepatitis and cholestasis in pediatric patients with ATD makes the accurate interpretation of obtained results difficult. Still, it seems reasonable to use APRI among other factors to select patients with higher risk of liver disease progression.

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