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Clinical, laboratorial and evolutionary aspects of pediatric patients with liver disease due to alpha 1-antitrypsin deficiency

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HIGHLIGHTS

- Jaundice is an important clinical sign that motivates referral to a specialist, but, in this study, it did not compromise survival with native liver in patients with alpha 1-antitrypsin deficiency.
- Patients with alpha 1-antitrypsin deficiency who develop portal hypertension had higher AST and APRI scores on admission.
- Patients with alpha 1-antitrypsin deficiency who develop portal hypertension have significant impairment of survival with native liver.

ABSTRACT – Background – Alpha 1-antitrypsin deficiency (AATD) is a hereditary codominant autosomal disease. This liver disease ranges from asymptomatic cases to terminal illness, which makes early recognition and diagnosis challenging. It is the main cause of pediatric liver transplantation after biliary atresia. **Objective –** To describe the clinical characteristics, as well as those of histologic and laboratory tests, phenotypic and/or genetic evaluation and evolution of a cohort of pediatric patients with AATD. **Methods –** This is a retrospective observational study of 39 patients with confirmed or probable AATD (without phenotyping or genotyping, but with suggestive clinical features, low serum alpha 1-antitrypsin (AAT) level and liver biopsy with PAS granules, resistant diastasis). Clinical, laboratory and histological variables, presence of portal hypertension (PH) and survival with native liver have been analyzed. **Results –** A total of 66.7% of 39 patients were male (26/39). The initial manifestation was cholestatic jaundice in 79.5% (31/39). Liver transplantation was performed in 28.2% (11/39) of patients. Diagnosis occurred at an average of 3.1 years old and liver transplantation at 4.1 years of age. 89.2% (25/28) of the patients with confirmed AATD were PI*ZZ or ZZ. The average AAT value on admission for PI*ZZ or ZZ patients was 41.6 mg/dL. All transplanted patients with phenotyping or genotyping were PI*ZZ (or ZZ). Those who were jaundiced on admission were earlier referred to the specialized service and had higher levels of GGT and platelets on admission. There was no significant difference in the survival curve when comparing cholestatic jaundiced to non-cholestatic jaundiced patients on admission. Comparing patients who did or did not progress to PH, higher levels of AST and APRI score at diagnosis (P=0.011 and P=0.026, respectively) were observed and in the survival curves patients with PH showed impairment, with 20.2% survival with native liver in 15 years. **Conclusion –** Jaundice is an important clinical sign that motivates referral to a specialist, but it does not seem to compromise survival with native liver. Patients progressing to PH had higher AST, APRi score on admission and significantly impaired survival with native liver. It is important to pay attention to these signs in the follow-up of patients with AATD.

Keywords – Alpha 1-antitrypsin deficiency, cholestasis, liver cirrhosis, portal hypertension.

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INTRODUCTION

Alpha 1-antitrypsin deficiency (AATD) is an inherited codominant autosomal genetic disease caused by the mutation in SERPINA1 gene with numerous genetic polymorphisms and more than 100 alleles already described[1].

It is one of the most prevalent genetic diseases worldwide, with approximately 3.4 million people presenting a combination of SS, SZ or ZZ[2] deficiency alleles. In Brazil, the estimated prevalence of ZZ mutation carriers is of approximately 6000 individuals[3]. Still, underdiagnosis and delayed diagnostic are challenges to be overcome in the management of AATD associated liver disease.

AATD implies low levels of circulating alpha 1-antitrypsin protein (AAT) leading to a predisposition for chronic obstructive pulmonary disease, probably caused by reduced inhibition of neutrophil elastase, a mechanism called "loss of function"[4].

On the other hand, the pathophysiology of liver disease is not associated with AAT protein deficiency, but to its abnormal polymerization and accumulation within hepatocytes, a mechanism called "toxic gain of function". The exact relationship between protein polymerization and liver injury is not fully understood. However, studies in animal models show that the accumulation of mutant protein can lead to mitochondrial damage and stimulate cell apoptosis[4-6].

Clinical manifestations of liver disease are varied, even in patients with the same phenotype or genotype. They range from persistently asymptomatic or subclinical cases to acute neonatal hepatitis or chronic liver disease progressing to cirrhosis with portal hypertension (PH), end-stage liver disease and death in the first years of life[7-11].

For the diagnosis, it is necessary to initially measure the serum level of alpha 1-antitrypsin. Confirmation is only possible through genotyping or phenotyping tests. Liver biopsy is not the gold standard, but it can contribute to the diagnosis, especially in countries like Brazil[4], where phenotyping or genotyping are unavailable in the public health system. Specificity of the diastasis resistant, PAS-positive granules finding can reach 94% in patients carrying the Z allele[12].

Despite the existence of ongoing promising clinical trials on new pharmacological treatments, liver transplantation is still the only healing treatment for liver disease due to AATD. This disease is the main indication for pediatric liver transplantation among the metabolic diseases that affect the liver[13-15].

There are few pediatric studies on the evolution of AATD[9,11]. In Brazil, there are no studies about the prevalence or evolution of the disease in pediatric population.

The aim of this study was to describe the clinical characteristics, laboratory tests, phenotypic and/or genetic evaluation, liver histopathology and evolution of a cohort of pediatric patients with AATD, searching for possible prognostic factors.

METHODS

This is a retrospective observational study. Thirty-nine patients were studied, regardless of race, color or sex, from 06/21/2000 to 07/31/2022. Data were reviewed and collected from medical records of patients assessed on the pediatric hepatology ambulatory of the Pediatric Gastroenterology section at Clinic's Hospital of Federal University of Minas Gerais (UFMG).

Inclusion criteria: patients with pediatric age (<18 years old) and liver disease with confirmed diagnosis of alpha 1-antitrypsin deficiency, through phenotyping or genotyping tests. Patients with reduced serum alpha 1-antitrypsin levels, suggestive clinical features and liver biopsy with positive PAS/ diastasis resistant granules (but without phenotyping or genotyping for AATD) were included in the separate analysis and classified as probable alpha 1-antitrypsin deficient. Exclusion criteria: patients whose phenotype or genotype was PI*MZ or MZ, patients in whom the diagnosis of AATD was performed after 18 years of age and patients or guardians who refused to participate in the study.

Variables surveyed were gender, age, comorbidities, follow-up start date, age at diagnosis of AATD, serum level of alpha 1-antitrypsin and laboratory tests at admission, identified phenotype/genotype, liver biopsy findings, presence of portal hypertension and progression to liver transplantation or death.

In neonates cholestatic jaundice was defined as direct bilirubin level above 1.0 mg/dL, as recom-

mended by the latest NASPGHAN/ESPGHAN guideline[16]. For older patients, the diagnosis was considered when total serum bilirubin was higher than 50 mmoL/liter (2.9 mg/dL) with a conjugate fraction of at least 20%[17]. Patients who presented complications such as clinical or ultrasound ascites and/or ultrasound signs of cirrhosis with PH and/or esophagogastric varices and/or digestive hemorrhage were considered to have evolved with PH[9,18].

Additionally, platelet count and aspartate aminotransferase-platelet ratio index (APRi), variables already described in the literature as PH predictive factors, were included in the analysis. This score was calculated[19]:

$$\bullet\rightarrow \text{APRi: } \frac{\frac{AST}{ULN}}{Platelets\left(\frac{10^9}{L}\right)} \text{X100(ULN=upper limit of normality)}$$

Microsoft® Excel® was used for database construction and initial analysis. Continuous variables, without normal distribution in Shapiro Wilk test, were described in medians, 1st quartile and 3rd quartile. Data with normal distribution were described by mean and standard deviation. Student t test was used to compare means for variables with normal distribution and Mann Whitney test for non-normal distribution. Categorical variables were described by absolute and percentage frequencies. Exact Pearson's chi-squared and asymptotic Pearson's chi-squared tests were used for comparisons. The Z test of proportions was used to compare two proportions. Significance probability was considered significant when less than 0.05 ($P \leq 0.05$). Survival with native liver Analyses were performed using Kaplan Meier method and the tests used to compare the curves were Log-rank test (when curves had few or no intersections) or Wilcoxon test (when curves had some intersections). Statistical analyses were performed using version 20 of the Statistical Package for the Social Sciences (SPSS®).

The research project was registered on Brazil Platform and approved by the Research Ethics Committee of the Federal University of Minas Gerais. Approval number 5.596.686 of August 22, 2022.

RESULTS

From the 39 analyzed patients, 66.7% were male (26/39). Only 10.2% (4/39) had a family history of consanguinity. The first clinical manifestation of the disease, and main reason which led to a specialized service referral, was cholestatic jaundice in 79.5% (31/39) of patients, followed by visceromegaly in 7.6% (3/39). Family screening led to a specialty referral in 5.1% (2/39) of cases. The median age at first assessment by the hepatology team was 3.2 months (mean age 1.5 years old) and at diagnosis (confirmed or probable) 1.8 years old (mean age 3.1).

It is noted that 85.1% (23/27) of patients with native liver were initially jaundiced. In 28.2% (11/39) of patients there was progression to end-stage liver disease and need for liver transplantation. In 72.7% (8/11) of these, the initial clinical manifestation was cholestatic jaundice. All transplant recipients who had phenotyping/genotyping analysis (5 out of 11) were PI*ZZ or ZZ and 54.5% (6/11) were female. The average age at which the transplant was performed was 4.1 and 72.7% (8/11) of these remain alive.

Histopathological analysis was performed in 28 patients. The finding of PAS+ / diastasis resistant granules was described in 80% (16/20) of the cases. These patients underwent biopsy at a median age of 1.5 (mean 2.3 years old). The median age at biopsy of patients with negative test for PAS+ / diastasis resistant granules was 1.9 months (mean 2.6 months). Liver fibrosis at diagnosis was identified in 83.3% (20/24) and inflammatory infiltrate in 84.2% (16/19). Other less frequently described findings were intracanalicular and intraductal cholestasis, hydropic degeneration (or ballooning hepatocytes), ductular reaction, steatosis, ductopenia and hepatocyte necrosis.

Analysis of the 39 patients with confirmed or probable AATD

When comparing patients with and without cholestatic jaundice on admission, we observed that patients whose initial manifestation was jaundice are earlier referred to the specialized service and have higher GGT and platelets on admission (with statistical significance). Degree of liver fibrosis, progression to PH and other laboratory tests showed no significant difference. Despite the median age for evolution to portal hypertension being lower in the jaundiced group, there was no statistical significance (TABLE 1).

TABLE 1. Comparison between clinical, laboratory, histological and evolution data of the 39 patients with confirmed or probable AATD, with or without cholestatic jaundice on admission.

Variables	Cholestatic jaundice (%)	Non-jaundiced (%)	Total (%)	*P*
	N=31 (79.5)	N=8 (20.5)	N=39 (100.0)	
Sex N (%)				
Male	18 (69.2)	8 (30.8)	26 (100.0)	0.035[1]
Female	13 (100.0)	0 (0.0)	13 (100.0)	
Age*				
Median (days/years)	83.5 / 0.23	798 / 2.1	99.5 / 0.27	0.005[2]
Q1;Q3	(57.75; 166.75)	(260.25; 1585.50)	(62.75; 294.25)	
AAT serum dosage*				
Median (mg/dL)	37.9	31	37.8	0.578[2]
Q1;Q3	31.50; 54.30	29.50; 63.25	30.50; 57.15	
Hemoglobin (g/dL)*				
Mean + standard deviation	10.66±1.93	11.97±2.35	10.86±2.06	0.113[3]
Platelets (/µL)*				
Mean + standard deviation	414.763±206.849	239.000±112.809	379.610±203.252	0.007[3]
AST (U/L)*				
Median	165.5	235	174	0.222[2]
Q1;Q3	124.00; 260.50	172.00; 240.00	131.00; 255.00	
ALT (U/L)*				
Median	101.5	165	115	0.005[2]
Q1;Q3	64.00; 145.25	141.00; 268.00	77.00; 162.00	
GGT (U/L)*				
Median	848	441.5	668	0.049[2]
Q1;Q3	256.00; 1406.00	129.50; 667.50	341.00; 1255.00	
INR*				
Median	1.1	1.09	1.09	0.925[2]
Q1;Q3	1.00; 1.32	1.02; 1.28	1.00; 1.30	
Albumin*				
Mean + standard deviation	3.83±0.66	3.77±1.01	3.82±0.73	0.849[3]
APRi*				
Mean + standard deviation	1.86±2.50	2.86±1.70	2.06±2.41	0.236[3]
Fibrosis degree in liver biopsy*				
Absent or mild to moderate	13 (86.7)	2 (13.3)	15 (100.0)	0.326[1]
Severe or cirrhosis	6 (66.7)	3 (33.3)	9 (100.0)	
Progression to portal hypertension				
Yes	13 (72.2)	5 (27.8)	18 (100.0)	0.432[1]
No	18 (85.7)	3 (14.3)	21 (100.0)	
Age of evolution for portal hypertension				
Median (days / years)	412 / 1.1	1152 / 3.1	560 / 1.5	0.140[2]
Q1;Q3	262.25; 683.00	458.50; 2634.50	280.00; 1383.50	

*Data collected upon admission. [1]Exact Pearson chi-square test; [2]Mann Whitney Test; [3]Student t test.

When comparing patients who did or did not evolve with PH, there was no statistically significant difference between gender, serum A1AT level or laboratory tests, except for AST and APRi score, which were higher on admission in patients who evolved with PH (P=0.011 and P=0.026, respectively) (TABLE 2). Admission APRi score was greater than 1.5 in 13 patients, 6 of which (46%) underwent liver transplantation. In those who evolved with portal hypertension, the median age at which this complication was observed was 1.5 years old, and the median age at which they reached the worst Child-Pugh classification was 7.

TABLE 2. Comparison between clinical and laboratory data of the 39 patients with confirmed or probable AATD with or without progression to portal hypertension.

Variables	Patients who evolved with portal hypertension (%)	Patients without portal hypertension (%)	Total (%)	*P*
	N=18 (46)	N=21 (54)	N=39 (100.0)	
Sex N (%)				
Male	11 (42.3)	15 (57.7)	26 (100.0)	0.496[1]
Female	7 (53.8)	6 (46.2)	13 (100)	
A1AT serum dosage *				
Median (mg/dL)	52.3	34.5	37.8	0.063[2]
Q1;Q3	29.00; 67.00	31.13; 40.75	30.50; 57.15	
Hemoglobin (g/dL)*				
Mean + standard deviation	10.89±1.92	10.84±2.21	10.86±2.06	0.939[3]
Platelets (/µL)*				
Mean + standard deviation	324.655±206.089	429.722±192.807	379.610±203.252	0.135[1]
AST (U/L)*				
Mean + standard deviation	257.24±131.90	159.95±67.07	204.65±111.90	0.011[1]
ALT (U/L)*				
Median	130	101.5	115	0.161[2]
Q1;Q3	92.00; 168.00	61.00; 151.75	77.00; 162.00	
GGT (U/L)*				
Median	718	668	668	0.817[2]
Q1;Q3	400.50; 1101.00	155.00; 1515.00	241.00; 1255.00	
INR*				
Median	1.1	1.08	1.09	0.551[2]
Q1;Q3	1.02; 1.32	1.00; 1.29	1.00; 1.30	
Albumin*				
Mean + standard deviation	3.60±0.78	4.01±0.65	3.82±0.73	0.110[1]
Total bilirubin (mg/dL)*				
Median	2.5	5.75	5.49	0.573[2]
Q1;Q3	1.25; 8.33	1.28; 7.35	1.25; 7.78	
Direct Bilirubin (mg/dL)*				
Median	1.7	4.05	3.8	0.988[2]
Q1;Q3	0.55; 6.12	0.29; 5.61	0.55; 5.84	
APRi*				
Mean + standard deviation	3.16±3.23	1.14±0.61	2.06±2.42	0.026[3]

*Data collected upon admission. [1]Student *t* test; [2]Mann Whitney test.

Analysis of 28 patients with confirmed AATD

Regarding the 28 patients with a confirmed diagnosis, 89.3% (25/28) were PI*ZZ or ZZ and 10.7% (3/28) were PI*SZ or SZ. PI*ZZ or ZZ patients had a mean serum A1AT dosage at diagnosis of 41.6 mg/dL, which was equivalent to a mean of 45.9% of the reference value.

Jaundiced patients were referred earlier to the pediatric hepatology service. On the other hand, there was no statistically significant difference between GGT levels, platelets and progression to PH. The presence of liver fibrosis was significantly higher in jaundiced patients (TABLE 3).

When comparing patients who did or did not

TABLE 3. Comparison between clinical, laboratory, histological and evolution data of the 28 patients with confirmed AATD, with or without cholestatic jaundice on admission.

Variables	Cholestatic jaundice (%)	Non-jaundiced (%)	Total (%)	*P*
	N=23 (82.1%)	N=5 (17.9)	N=28 (100.0)	
Sex N (%)				
Male	14 (73.7)	5 (26.3)	19 (100.0)	0.144[1]
Female	9 (100.0)	0 (0.0)	9 (100.0)	
Age				
Median (days / years)	68 / 0.18	281 / 0.77	91 / 0.25	0.033[2]
Q1;Q3	57.00; 106.00	173.50; 1.364.00	58.25; 256.75	
Serum dosage of A1AT*				
Median (mg/dL)	37.8	30	37	0.219[2]
Q1;Q3	32.00; 44.90	28.50; 54.00	31.00; 44.90	
Hemoglobin (g/dL)*				
Mean + standard deviation	10.64 ±2.09	12.58±2.17	10.93±2.18	0.102[3]
Platelets (/µL)*				
Mean + standard deviation	409.798±193.355	251.500±119.884	385.360±191.095	0.130[3]
AST (U/L)*				
Mean + standard deviation	158.04±75.32	204.00±39.91	164.85±72.53	0.250[3]
ALT (U/L)*				
Median	93	175.5	102	0.020[2]
Q1;Q3	60.00; 130.00	129.75; 247.50	64.00; 155.00	
GGT (U/L)*				
Median	795.5	446	705.5	0.177[2]
Q1;Q3	345.25; 1806.25	124.00; 892.50	334.00; 1576.75	
INR*				
Median	1.05	1.22	1.06	0.598[2]
Q1;Q3	1.00; 1.21	1.11; 1.28	1.00; 1.28	
Albumin*				
Mean + standard deviation	3.99±0.65	4.25 ±0.79	4.04±0.66	0.492[3]
APRi*				
Mean + standard deviation	1.22±0.84	2.35±1.04	1.39±0.95	0.112[3]
Fibrosis degree in liver biopsy*				
Absent or mild to moderate	11 (100.0)	0 (0.0)	11 (100.0)	0.033[1]
Severe or cirrhosis	1 (33.3)	2 (66.7)	3 (100.0)	
Progression to portal hypertension				
Yes	6 (66.7)	3 (33.3)	9 (100.0)	0.290[1]
No	17 (89.5)	2 (10.5)	19 (100.0)	
Age of evolution for portal hypertension				
Median (days / years)	435 / 1.2	1152 / 3.1	512.5 / 1.4	0.4562
Q1;Q3	259.00; 590	720.00; 2403.00	266.25; 3028.50	

*Data collected upon admission. [1]Exact Pearson chi-square test; [2]Mann Whitney Test; [3]Student *t* test.

progress to PH, among the 28 with a confirmed diagnosis of AATD, no statistically significant difference was observed between clinical, laboratory and evolution data (TABLE 4).

Survival analysis

Patients with AATD had an impact on survival with native liver over the years (FIGURES 1A and 1B). Between jaundiced and non-jaundiced patients, there was no statistically significant difference between the survival curves with 39 or 28 patients (Figures 1C and 1D). In patients with progression to PH, survival with native liver was impacted with statistical significance in the confirmed/probable AATD group (P=0.000) and in the confirmed AATD group (P=0.011) (FIGURES 1E and 1F).

TABLE 4. Comparison between clinical and laboratory data of the 28 patients with confirmed AATD with or without progression to portal hypertension.

Variables	Patients who evolved with portal hypertension (%) N=9 (32)	Patients without portal hypertension (%) N=19 (68)	Total (%) N=28 (100.0)	*P*
Sex N (%)				
Male	11 (42.3)	15 (57.7)	26 (100.0)	0.496[1]
Female	7 (53.8)	6 (46.2)	13 (100)	
A1AT serum dosage*				
Mean + standard deviation	50.59±24.17	37.33±11.32	41.75±17.44	0.150[3]
Hemoglobin (g/dL)*				
Mean + standard deviation	11.37±2.18	10.71±2.21	10.93±2.18	0.468[3]
Platelets (/µL)*				
Mean + standard deviation	294.375±146.394	433.529±198042.96	385.360±191.095	0.077[3]
AST (U/L)*				
Mean + standard deviation	177.56±78.72	158.50±70.72	164.85±72.53	0.530[3]
ALT (U/L)*				
Median	118	101.5	102	0.440[2]
Q1;Q3	77.00; 168.00	58.75; 145.25	64.00; 155.00	
GGT (U/L)*				
Median	588	743	705.5	0.893[2]
Q1;Q3	344.50; 1383.50	186.50; 1727.00	334.00; 1576.75	
INR*				
Median	1.05	1.07	1.06	0.828[2]
Q1;Q3	1.00; 1.28	1.00; 1.32	1.00; 1.28	
Albumin*				
Median	3.7	4	4	0.646[2]
Q1;Q3	3.60; 4.70	3.70; 4.50	3.68; 4.50	
Total bilirubin (mg/dL)*				
Mean + standard deviation	4.48 ±3.48	5.49±3.37	5.15±3.38	0.474[3]
Direct bilirubin (mg/dL)*				
Mean + standard deviation	3.39 ± 2.91	3.89 ±2.90	3.72±2.86	0.674[3]
APRi*				
Mean + standard deviation	1.97±1.23	1.09±0.60	1.39±0.95	0.070[3]

*Data collected upon admission. [1]Exact Pearson chi-square test; [2]Mann Whitney Test; [3]Student *t* test.

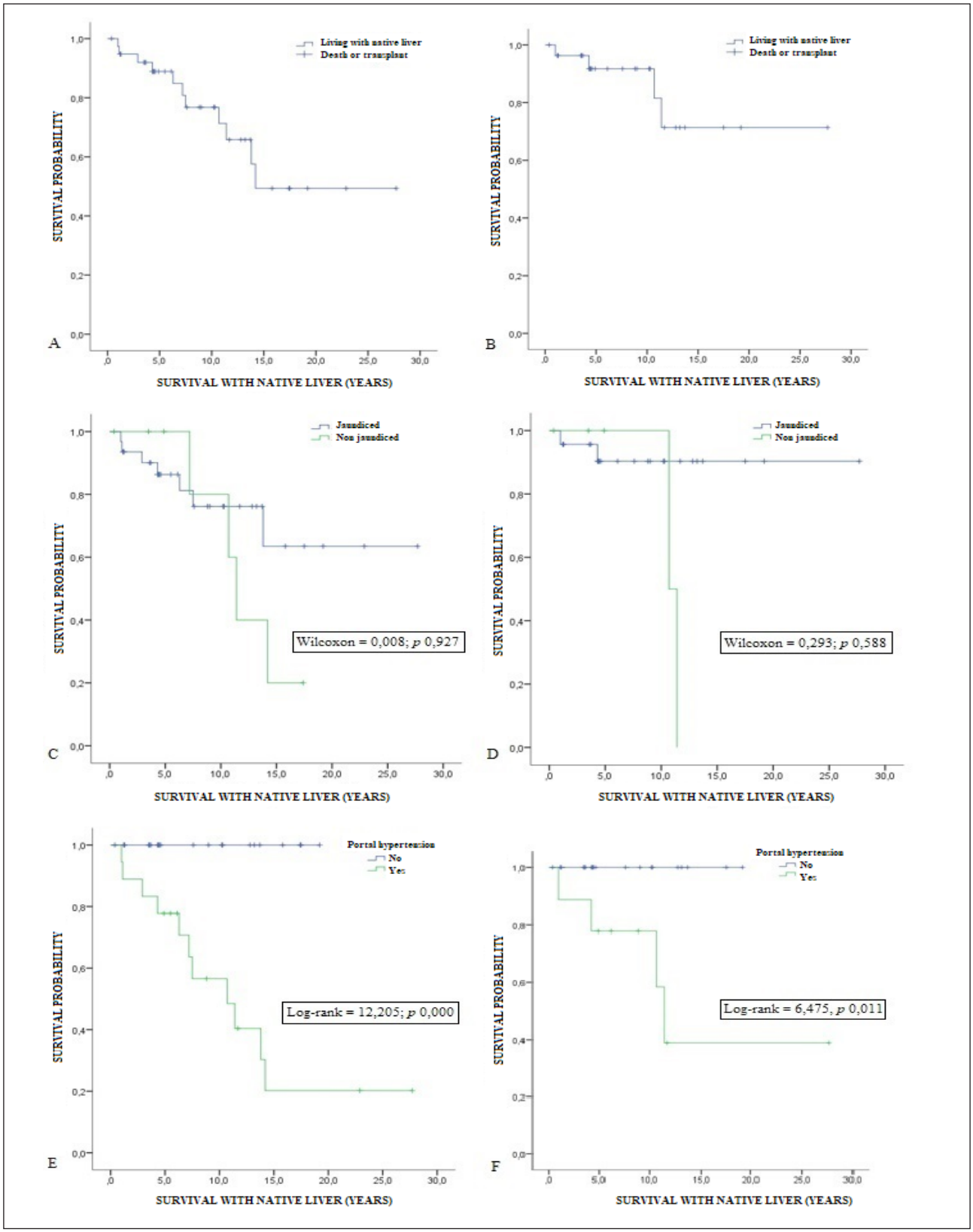

FIGURE 1. Kaplan-Meier survival curves with native liver. A: confirmed or probable AATD (39 patients). B: confirmed AATD (28 patients). C: Comparison between jaundiced and non-jaundiced patients with confirmed or probable AATD (39 patients). D: Comparison between jaundiced and non-jaundiced patients with confirmed AATD (28 patients). E: Comparison between patients who progressed or not to PH with confirmed or probable AATD (39 patients). F: Comparison between patients who progressed or not to PH with confirmed AATD (28 patients).

DISCUSSION

The wide spectrum of clinical presentation and evolution of patients with the same AATD phenotype or genotype (including siblings) strongly suggests the presence of genetic or epigenetic modifiers that are still unknown. Little is known about risk factors that could predict the progression to liver disease and the prognosis of these patients[18,20].

There are heterogeneous information about potential clinical or laboratory risk factors in international literature. In cohorts with adult patients, male sex, over 50 years old, PI*ZZ phenotype, repeated elevation of liver enzymes, superimposed viral hepatitis and presence of diabetes have been identified as potential risk factors for liver disease and severe liver disease[10,21].

In this study, considering the largest group of 39 patients, a predominance of cholestatic jaundice as the initial manifestation and of the PI*ZZ (or ZZ) phenotype (genotype) was observed, including in patients who progressed to HP and transplantation. In the group that presented cholestatic jaundice as the initial manifestation, there was a predominance of males and higher values of GGT and platelets on admission, with statistical significance. In the group that progressed to PH, only AST elevation on admission was statistically significant.

In pediatric age, the presence of neonatal cholestatic jaundice, neonatal cholestasis or neonatal hepatitis seems to be almost unanimous as the initial clinical presentation of AATD. There are studies showing that this presentation may be associated with progression to severe liver disease, with portal hypertension and need for transplant. However, Teckman et al.[9] (2015) suggest that this may be a weak association, since many patients who are initially cholestatic may have a good evolution, sometimes with spontaneous improvement over time. The PI*ZZ phenotype has also been associated with moderate to severe disease and constitutes the majority of patients with AATD liver disease[9,11-22].

Male sex has been predominant in most adult and pediatric cohorts both in patients with liver disease due to AATD and in those transplanted due to the same diagnosis. However, this predominance is not always statistically significant[9-11,23].

Regarding laboratory alterations, data in the literature seem to reflect the progression of liver disease. In Francavilla et al.[22] (2000), similarly to this study, AST was significantly higher at admission in patients who evolved with severe liver disease with transplant indication. In Pferdmenges et al.[24] (2013), elevation of bilirubin, AST, GGT and prothrombin activity demonstrated correlation with the need for liver transplantation and/or death. In Teckman et al.[9] (2015), patients with PH were more likely to have higher AST, ALT, GGT and INR.

APRi score correlates significantly to fibrosis stage and cirrhosis in patients with chronic C hepatitis. Despite being a low-cost and non-invasive method, the use of this score alone, in patients with AATD is still not well established. Combination with other non-invasive tests like transient elastography can contribute to its use in clinical practice[19,25].

In this study, there was an interval of 1.6 years from the first evaluation by the pediatric hepatology team to the diagnosis, which occurred approximately at 3.1 years old, a higher age than other cohorts such as the North American cohort by Teckman et al.[9] (2015), in which the diagnosis occurred at a mean age of 1.7 years, and the French cohort by Ruiz et al.[11] (2019), in which the diagnosis of most patients occurred at less than 2 months old (with a mean age of 1.8 years).

Despite the above mentioned, the delay or failure in diagnosis is still a serious problem in the management of patients with liver disease due to AATD, even in developed countries. In a North American study by Stoller et al.[26] (2005), two cohorts (in 1994 and 2003) were evaluated for the time, in years, of delay in the diagnosis of AATD. A delay of 7.2±8.3 years was identified in the 1994 cohort and of 5.3±8.5 years in the 2003 cohort. A retrospective analysis of histopathological material from 1473 adults transplanted in downtown Cleveland (United States) showed that, in more than 30% of the AATD evaluated cases, the diagnosis was performed after the transplant[27].

The higher age at diagnosis observed in this study can be explained by the delay in referral to a specialist due to lack of knowledge about the disease or even because of its wide variability in clinical presentation. Besides, this study was conducted in a developing country, in which the general population

doesn't have access to high-cost tests such as phenotyping, genotyping for AATD or highly complex procedures such as ultrasound-guided liver biopsy which are also restricted to large centers.

In this study, patients were categorized into confirmed/probable or confirmed diagnosis of AATD, since 11 patients had low serum levels of AAT, typical clinical features and histopathology, but without available phenotyping or genotyping results. In spite of the fact that it is not an ideal method, liver biopsy can contribute to the diagnosis of AATD. Histopathological changes in childhood can be varied and nonspecific, such as ductopenia, inflammatory infiltrate, varying degrees of fibrosis, steatosis, hepatocellular necrosis, presence of giant cells, among others. The finding of positive diastasis resistant PAS granules favors the diagnosis but can be difficult to detect in the first months of life[18,23].

In the study by Clausen et al.[12] (1984), the finding of larger than 1 micrometer PAS + / diastasis resistant granules was associated with a specificity of 77% for the presence of the Z allele and the finding of larger than three micrometers globules, although infrequent, was associated with a specificity of 94% for the presence of the Z allele. A retrospective cohort by Comba et al.[23] (2018) concluded that in the biopsies, the main histopathological finding was inflammation, and all but one patient had PAS-positive, diastasis resistant granules in the liver tissue, emphasizing the importance of this data in the suspected diagnosis of AATD.

A percentage of 88.9% from the 39 patients expresses the survival with native liver in 5 years. In this study, no statistically significant difference was observed in survival with native liver between patients whose initial clinical manifestation was the presence or absence of cholestatic jaundice. On the other hand, patients who progressed to PH had a significant impact, with a survival with native liver of 77.8% in 5 years, 56.6% in 10 years and only 20.2% in 15 years. In the retrospective cohort of Pferdmenges et al.[24] (2013) 53 PI*ZZ pediatric patients were evaluated and survival analysis showed that in 5 years 77.3% of patients were alive with native liver, similarly to the present study.

Transplant was indicated for 28% of the patients in this study, with a median age of 4.1 years old at transplantation. Data are similar to those of Francavilla et al.[22] (2000), in which there was indication for transplantation in 24.1% of patients, and the median age at the procedure was 3.8 years old. In the cohort of Chu et al.[10] (2016), almost all children with AATD who underwent liver transplantation were younger than 5 years old, so that age (<5 years old) seems to be a risk factor for progression to transplantation.

AATD is the second cause for transplant indication among children under 10 years of age in this pediatric hepatology service, second only to Biliary Atresia (BA) (data not presented in this study). A study by Esquivel et al.[28] (1987) involving 250 transplanted children had already observed AATD as the second main cause for transplant indication, also second to BA. Similar results were found in subsequent studies such as those of Casavilla et al.[13] (1994), Migliazza et al.[14] (2000) and Pham, Miloh[15] (2018), in which AATD was the main indication for pediatric liver transplantation among metabolic diseases and the second general cause (after BA).

In this study, 72% (8/11) of patients remain alive after transplantation and 28% (3/11) died after the procedure. It was not the objective of the study to analyze post-transplant survival. However, it is important to emphasize that liver transplantation remains the only curative treatment for AATD. Over the years, with the improvement of surgical techniques and the advent of immunosuppressants such as Tacrolimus and Ciclosporin, transplanted pediatric patients can achieve post-transplant survival above 90% at 1, 5 and 10 years, being a good option for patients who evolve for end-stage liver disease[14,15].

As positive aspects of this study, there is the fact that, despite having been conducted in a single center, the casuistry of 39 patients is relevant in comparison with other already published cohorts. The results were similar to those of the available international literature.

As a weakness of this study, it is a retrospective analysis, which makes data losses expected. Furthermore, in 11/39 (28.2%) patients, a probable diagnosis of AATD was obtained, but not confirmed.

A multicenter study could be more representative of the reality of this disease in Brazil. In addition, it is important to mention the lack of larger studies that investigate practices that can effectively modify the

natural history of liver disease so that patients are earlier referred to a specialty and do not miss the ideal time for indication of liver transplantation.

CONCLUSION

This study addressed the experience of the Pediatric Hepatology team at UFMG Clinic's Hospital in the follow-up of patients with AATD, one of the most common genetic diseases in the world, with heterogeneous characteristics that imply in delay and difficulty in diagnosis worldwide.

Despite the difficulty of associating clinical and laboratory factors that constitute predictors of a worse prognosis, this study showed that attention should be given to younger than five years old children, with the PI*ZZ phenotype (or ZZ genotype), male and with altered AST upon admission.

Although cholestatic jaundice is the main initial clinical presentation of AATD, it was not associated with worse survival with native liver, when compared with its absence. Even so, it is an important clinical data with regard to early referral to a specialty.

Patients with progression to PH have significantly lower native liver survival compared to patients without PH. Therefore, these patients should receive more frequent follow-up and special care so as to avoid exposure to risky situations.

Author's contribution

Queiroz TCN, Fagundes EDT, Rodrigues AT and Ferreira AR: designed the work. Queiroz TCN, Rodrigues AT and Costa MP wrote the project and obtained approval from the ethics committee. Queiroz TCN and Costa MP: collected, analyzed, interpreted the data and wrote the initial manuscript. Fagundes EDT, Rodrigues AT and Ferreira AR: supervised all stages, reviewed and edited the manuscript. All authors approved the final version as submitted.

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Costa MP, Ferreira AR, Rodrigues AT, Fagundes EDT, Queiroz TCN. Aspectos clínicos, laboratoriais e evolutivos de pacientes pediátricos com doença hepática por deficiência de alfa 1-antitripsina. Arq gastroenterol. 2023;60(4):438-49.

RESUMO – Contexto – Deficiência de alfa 1-antitripsina (DAAT) é uma doença hereditária, de caráter autossômico codominante. A apresentação da doença hepática varia desde casos assintomáticos até doença terminal, o que dificulta reconhecimento e diagnóstico precoces. É a principal causa de transplante hepático pediátrico após atresia de vias biliares. **Objetivo –** Descrever as características clínicas, de exames laboratoriais, histológicos, avaliação fenotípica e/ou genética e sobrevida de uma coorte de pacientes pediátricos com DAAT. **Métodos –** Estudo observacional retrospectivo de 39 pacientes com diagnóstico de DAAT confirmada ou provável (sem fenotipagem ou genotipagem, mas com clínica sugestiva, baixo nível sérico de alfa 1-antitripsina (A1AT) e biópsia hepática com grânulos PAS, diástase resistentes). Variáveis clínicas, laboratoriais, histológicas, presença de hipertensão portal (HP) e sobrevida com fígado nativo foram analisadas. **Resultados –** Dos 39 pacientes, 66,7% eram do sexo masculino (26/39). A manifestação inicial foi icterícia colestática em 79,5% (31/39). Em 28,2% (11/39) houve necessidade de transplante hepático. O diagnóstico ocorreu com uma idade média de 3,1 anos e, o transplante hepático, 4,1 anos. Dos pacientes com DAAT confirmada, 89,2% (25/28) eram PI*ZZ ou ZZ. O valor médio de A1AT na admissão de pacientes PI*ZZ ou ZZ foi 41,6 mg/dL. Todos os transplantados com fenotipagem ou genotipagem eram PI*ZZ (ou ZZ). Os ictéricos à admissão foram referenciados mais cedo ao serviço especializado e apresentaram níveis mais elevados de GGT e plaquetas à admissão. Não houve diferença significativa na curva de sobrevida ao compararmos icterícia colestática ou não à admissão. Ao comparar os pacientes que progrediram ou não para HP, observou-se níveis mais elevados de AST e APRI escore ao diagnóstico (P=0,011 e P=0,026, respectivamente) e, nas curvas de sobrevida, pacientes com HP apresentaram comprometimento, com 20,2% de sobrevida com fígado nativo em 15 anos. **Conclusão –** Icterícia é um sinal clínico importante que motiva o encaminhamento ao especialista, mas parece não comprometer a sobrevida com fígado nativo. Pacientes com evolução para HP tiveram AST e escore APRi mais elevados à admissão e comprometimento significativo da sobrevida com fígado nativo. Importante atentar a esses sinais no seguimento de pacientes com DAAT.

Palavras-chave – Deficiência de alfa 1-antitripsina; colestase; cirrose hepática; hipertensão portal.

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