Hepatic Fibrosis: A Manifestation of the Evolution of Liver Disease in Patients with Ataxia-Telangiectasia

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Abstract

Background: Ataxia-telangiectasia (A-T) is a DNA repair disorder characterized by changes in several organs and systems. Advances in clinical protocols have resulted in increased survival of A-T patients, however disease progression is evident, mainly through metabolic and liver changes. We aimed to identify the frequency of significant hepatic fibrosis in A-T patients and to verify association with metabolic alterations and degree of ataxia.

Results: Dyslipidemia was observed in 16/25 (64%), diabetes in 4/22 (18%), insulin resistance in 5/17 (29%), hepatic steatosis in 13/20 (65%) and suggestive of significant hepatic fibrosis in 5/25 (20%). Patients in the group with significant hepatic fibrosis were older ($p<0.001$), had lower platelet values ($p=0.027$), albumin ($p=0.019$), HDL-c ($p=0.013$) and Matsuda index ($p=0.044$); and high values of LDL-c ($p=0.049$), AST ($p=0.001$), alanine aminotransferase ($p=0.002$), gamma-glutamyl transferase ($p=0.001$), ferritin ($p=0.001$), 120-minutes glycemia by OGTT ($p=0.049$), HOMA-AD ($p=0.016$) and degree of ataxia ($p=0.009$).

Conclusions: A suggestive diagnosis of significant hepatic fibrosis was observed in 20% of A-T patients which was associated with changes in liver enzymes, ferritin, increased HOMA-AD and with severity of ataxia compared to patients without hepatic fibrosis.

Background

Ataxia-telangiectasia (A-T) is a DNA repair disorder characterized by changes in several organs and systems including progressive cerebellar degeneration, immunological changes, recurrent sinopulmonary infections, radiation sensitivity, increased risk of cancer, especially of lymphoid origin, growth retardation and pubertal development, insulin-resistant diabetes and, more recently, chronic liver disease [1–5].

A-T is an autosomal recessive condition caused by pathogenic variants in the *ATM* (ataxia telangiectasia mutated) gene, located on chromosome 11q22-23, that cause failure in the functioning of the ATM protein, a serine/threonine kinase, responsible for maintaining genomic stability, recognizing/correcting errors in DNA duplication, and controlling cell cycle [6]. Chronic oxidative stress due to impaired function or absence of ATM protein explains most of the characteristic symptoms of the disease [7, 8].

Despite advances in the treatment and control of the disease, enzymes such as gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increase with age, suggesting liver injury [5, 9, 10]. Publications addressing liver disorders in A-T patients are scarce, mostly are case reports. Histopathological findings show suggestive of non-alcoholic steatohepatitis (NASH), liver cirrhosis and hepato-cellular carcinoma (HCC) [11–16].

Although histopathological examination is considered the gold standard for the evaluation of necroinflammation and fibrosis, there are proposals for the use of indices/scores derived from formulas with biomarkers and liver imaging as noninvasive alternatives to the biopsy procedure; interesting

proposal especially for A-T patients [17, 18]. These noninvasive methods have been recommended for the identification of hepatic fibrosis, with varied availability and accuracy and that allow longitudinal evaluation and monitoring the liver disease progression [19–23].

To our knowledge, there are no publications to date evaluating imaging and liver fibrosis biomarkers in A-T patients. Thus, the aim of this study was to identify the frequency of significant hepatic fibrosis and to verify an association with metabolic changes and the degree of ataxia in A-T patients.

Methods

This is a cross-sectional study that included 25 A-T patients from both genders, aged between 5 and 31 years, who met the diagnostic clinical criteria of the European Society for Immunodeficiencies (ESID), under a multidisciplinary follow-up at the Division of Allergy, Clinical Immunology, Rheumatology of the Department of Pediatrics of Universidade Federal de São Paulo (UNIFESP/EPM) [24]. Individuals undergoing oncological treatment, using hepatotoxic drugs or those with hepatitis B or C were excluded. The outpatient clinic currently follows 26 A-T patients and only one patient was excluded from the study for undergoing cancer treatment.

The study was approved by UNIFESP Research Ethics Committee (0081/2018). All the caregivers of patients signed an informed consent to be enrolled in this study.

Anthropometric and pubertal development assessment

Anthropometric measurements included weight, height and skinfolds (tricipital, bicipital, subscapular and suprailiac) and the mid-upper arm circumference and waist circumference (WC) [25, 26]. The patients who were unable to stand upright were weighed on a digital wheelchair scale (Micheletti® electronic weighing platform for up to 500 kg). Recumbent height measurements were taken in supine position on a flat, firm surface by using a non-extensible tape (in millimeters).

For nutritional status classification, body mass index (BMI)-for-age and height-for-age z-scores for children and adolescents were calculated. Adults were classified according to BMI [25, 27]. The sum of the skinfold thickness was used to estimate the body fat percentage [28–31].

The WC was classified as altered when the WC to height ratio (WHtR) was equal or higher than 0.5 [32, 33]. Mid-upper arm circumference combined to the tricipital skinfold was used to estimate the mid-upper arm muscle circumference (MUAMC) [26, 31].

The stage of pubertal development was self-assessed according to Marshall & Tanner [34].

Neurological assessment

The International Cooperative Ataxia Rating Scale (ICARS) was applied in the adapted and validated version for the Brazilian culture to evaluate ataxia severity in all patients by a skilled physical therapist.

ICARS has 19 items subdivided into four subscales with a maximum score of 100: posture and gait disturbances; kinetic functions; speech disorders and oculomotor disorders. For the severity classification, the following cut-off points were adopted: mild ataxia (1 to 30 points), moderate ataxia (31 to 60 points) and severe ataxia (> 60 points) [35].

Laboratory tests

Blood was collected, after an 8-hour fasting, by peripheral venous puncture for biomarker analysis. All analyses were performed with standardized methods and according to good practices in clinical analyses.

Liver injury biomarkers

ALT, AST, GGT, total proteins and fractions, alkaline phosphatase (ALKP), alpha-fetoprotein (AFP) and cytokeratin-18 (CK-18): ELISA (Human Cytokeratin 18 ELISA Kit. Elabscience Biotechnology Inc.®. USES. Variation: 6.25-400 mIU/mL. Sensitivity: 3.75 mIU/mL. Accuracy: CV < 10%).

Indices/scores based on biomarkers for evaluation of hepatic fibrosis were calculated, adopting the following cut-off points as suggestive of fibrosis: AST to platelet ratio index (APRI): >0.50; nonalcoholic fatty liver disease fibrosis score (NFS): >0.676 and BARD score when achieved >2 points [36–38].

Inflammation biomarkers

High-sensitivity C-reactive protein (hs-CRP); Ferritin; Serum amyloid-A protein (SAA): ELISA (Human SAA ELISA Kit. Thermo Fisher Scientific Inc.®. Austria, Range: 0-600 ng/mL. Sensitivity: <4 ng/mL. Inter-assay accuracy: CV 7.4% and intra-assay: 6.1%); Tumor necrosis factor alpha (TNF-alpha): ELISA (Human TNF alpha (Total) ELISA Kit. Thermo Fisher Scientific Inc.®. Austria. Sensitivity: 5.0 pg/mL. Inter-assay accuracy: CV 8.1% and intra-assay: 7.7%) and Adiponectin: ELISA (Human Adiponectin ELISA Kit. Thermo Fisher Scientific Inc ®. Austria. Sensibility: 0.012ng/mL, inter-assay accuracy: CV 3.1% and intra-assay: 4.2%).

Lipid metabolism biomarkers

Triglycerides (TG); total cholesterol (TC); low-density lipoprotein (LDL-c); high-density lipoprotein of cholesterol (HDL-c) and non-HDL-c cholesterol (NHDL-c) which was calculated by subtracting the TC values from the HDL-c values.

For classification, the cut-off points suggested by the American Academy of Pediatrics and the National Cholesterol Education Program (NCEP) were adopted [39, 40]. The NHDL-c was classified according to Bogalusa and the NCEP [40, 41].

Glucose metabolism biomarkers

The oral glucose tolerance test (OGTT) was performed with insulin dosage. After an 8-hour fast, 1.75 g/kg of dextrose (maximum dose of 75 g) was administered orally. Blood samples for glycemic and

insulin curves were obtained immediately after dextrose intake, in fasting and at 30, 60, 90 and 120-minutes intervals.

Glucose intolerance was considered when values between 140 mg/dL and 199mg/dL were found in 120 minutes. Diabetes was considered when fasting or at 120 minutes, values equal to or greater than 126mg/dL and equal to or greater than 200 mg/dL, respectively [42].

Insulin resistance (IR) was assessed using the following indices: Homeostasis Model Assessment - Insulin Resistance (HOMA-IR), Homeostasis Model Assessment - Adiponectin (HOMA-AD) and Matsuda that estimates whole-body insulin sensitivity [43–45]. For HOMA-AD classification, the cut-off points >8.6 for children and >14.3 for adolescents and adults were considered as suggestive of IR [46].

Liver imaging tests

Hepatic ultrasonography

Ultrasonography was performed for grading liver steatosis. The examination was performed by a single examiner (radiologist) using GE healthcare equipment, Logiq P6 model, 5 MHz multifrequency convex transducer. The changes in the liver parenchyma were stratified in the form of score (1-9): normal liver (0), slight diffuse steatosis (1-3), moderate (4-6) and accentuated (7-9). This classification uses as parameters the liver echogenicity in comparison with renal parenchyma and posterior sound attenuation in the liver parenchyma, which can be determined by the degree of visibility of the diaphragm and hepatic vessels [47].

Transient elastography

The transient elastography (TE) by FibroScan® (Echosens, Paris, France) was performed by an examiner (hepatologist) for the grading hepatic fibrosis, being obtained the liver stiffness measurement (LSM), expressed in kilopascals (kPa) and controlled attenuation parameter (CAP - dB/m) which provides an estimate of the proportion of hepatocytes affected by steatosis [48–51].

After a 2-hours-minimum fast, the patients were put in dorsal decubitus, with the right arm raised to facilitate access to the right hepatic lobe. A M-size probe was positioned between the 9th and 11th intercostal spaces between the anterior and middle axillary lines. In each examination, to obtain at least 10 valid measurements, a maximum of 20 measurements were performed.

For reliability analysis of the TE, the following parameters were used: success rate (SR) which would be the equivalent of the quotient between the number of valid measurements and the total number of obtained measurements expressed in percentage and interquartile range to median of measurements ratio (IQR/Md).

The following reliability criteria were adopted: minimum of 10 valid measurements; $SR \geq 60\%$; $IQR/Md < 30\%$ for any liver stiffness value; and $IQR/Md > 30\%$ for liver stiffness values below 7.1 kPa [52]. TE results that did not meet these criteria were disregarded.

A-T patients who presented by $TE \geq 7$ kPa (cutoff point used for NAFLD) or alteration of the APRI and one of the scores evaluated (NFS or BARD) simultaneously were considered with significant liver fibrosis [19, 36–38]. TE results were assessed and interpreted along with the clinical and laboratory aspects of each patient.

Statistical analysis

Data were entered and consolidated in an Excel spreadsheet (Office Microsoft ®) and analyzed using the statistical package SPSS 19.0 (IBM®). Categorical variables were presented as absolute and percentage values. Continuous variables were analyzed for its normality using Shapiro-Wilk test. For comparisons between the two groups of patients, with or without significant liver fibrosis, the variables with parametric distribution were presented in the form of mean and standard deviation and compared by the independent t-Student test and the variables with non-parametric distribution were presented as median (minimum and maximum) and compared by the two-tailed Mann-Whitney U test. Spearman's correlation coefficient was used to assess the correlations. The statistical significance level of 5% ($p<0.05$) was adopted.

Results

Mean age of A-T patients ($n = 25$) was 10.9 (± 3.8) years, 16/25 (64%) males. The mean age at A-T diagnosis and at the initial appearance of symptoms were 5.0 (± 3.6) years and 10 (± 4.3) months, respectively. At the time of evaluation, 17/25 (68%) received regular intravenous immunoglobulin infusion, 8/25 (32%) used prophylactic antibiotics and 3/25 (12%) had chronic pneumopathy. According to the ICARS scale used to assess ataxia 13/25 (52%) were classified as having moderate ataxia.

Regarding nutritional status, 8/25 (32%) were malnourished, only 1/25 (4%) were overweight and 8/19 (42%) had short stature for age. According to body composition, only 4/24 (16.7%) had a low percentage of body fat. However, lean mass impairment was observed in 13/24 (54%) of the patients. Regarding pubertal development 8/25 (32%) were pubescent.

According to metabolic biomarkers, 16/25 (64%) had dyslipidemia, 4/22 (18%) were diabetic (three diagnosed by OGTT performed in this study), 5/17 (29%) had IR according to HOMA-AD and 5/25 (20%) had values equal to or greater than twice the upper limit of normal for AST and ALT enzymes. Hepatic steatosis by ultrasonography was found in 13/20 (65%) and suggestive diagnosis of significant liver fibrosis in 5/25 (20%) of A-T patients. TE result of only one patient was disregarded for not meeting the adopted reliability criteria. Table 1 shows the characteristics of A-T patients.

Table 1. Characteristics of the patients with Ataxia-telangiectasia

Four of the five A-T patients with suggestive diagnosis of significant liver fibrosis underwent TE. Three presented moderate steatosis (grade 2), two had no steatosis, four were diabetic, three had IR and all had dyslipidemia. Regarding nutritional status, only one was malnourished and four had lean mass

impairment. Table 2 shows the values of the parameters obtained by TE and the suggestive scores of liver fibrosis in patients considered to have suggestive diagnosis of significant liver fibrosis.

Table 2. Values of the parameters of the transient elastography and liver fibrosis scores in patients with suggestive diagnosis of significant liver fibrosis

A significant and direct correlation was observed between the median LSM obtained by TE and age ($\rho=0.717$; $p<0.001$), GGT ($\rho=0.578$; $p=0.006$), ICARS score ($\rho=0.435$; $p=0.049$), NFS ($\rho=0.590$; $p=0.005$), HOMA-AD ($\rho=0.485$; $p=0.041$) and indirect with adiponectin ($\rho=-0.613$; $p=0.003$); a fact not observed for the APRI ($\rho=0.432$; $p=0.051$) and ALT ($\rho=0.417$; $p=0.060$). Figure 1 shows the correlation between the median LSM with the HOMA-AD, NFS and the ICARS score.

Figure 1 Scatter plot for the correlation of the liver stiffness measurement (LSM) values with the HOMA-AD (Homeostasis Model Assessment – Adiponectin) (a), nonalcoholic fatty liver disease fibrosis score (NFS) (b), and International Cooperative Ataxia Rating Scale (ICARS) (c). (n=21). *Significance level of the Spearman correlation coefficient. Cut-off point ≥ 7 kPa adopted for the liver fibrosis (dotted line).

A-T patients were divided into two groups according to the presence or absence of suggestive of significant liver fibrosis to compare the variables evaluated in this study. A significant difference was found between groups for age ($p<0.001$), MUAMC ($p<0.001$), WC ($p=0.008$), ICARS score ($p=0.009$), platelets ($p=0.027$), albumin ($p=0.019$), HDL-c ($p=0.013$), LDL-c ($p=0.049$), AST ($p=0.001$), ALT ($p=0.002$), GGT ($p=0.001$), ferritin ($p=0.001$), 120-minutes glycemia ($p=0.049$), Matsuda index ($p=0.044$) and HOMA-AD ($p=0.016$) (Table 3).

Table 3. Comparison of the patients with Ataxia-telangiectasia according to the presence or absence of a suggestive of significant liver fibrosis

Liver biomarkers, inflammation and HOMA-IR, HOMA-AD and Matsuda indices were compared between patients with and without liver steatosis assessed by ultrasound, with no statistically significant difference being observed between groups for any of the variables.

In calculating the accuracy of the ultrasound assessment of steatosis as a predictor of significant liver fibrosis, a sensitivity of 60% (CI95% 14.7-94.7 and a specificity of 33% (CI95% 11.8-61.6) was observed. This finding suggests that the presence of hepatic steatosis on ultrasound does not seem to contribute to the screening of hepatic fibrosis in these patients.

Regarding the CAP values obtained by the TE there was no significant difference between patients without and with a suggestive diagnosis of significant fibrosis, although the second group had a higher mean of the CAP values (194.7 ± 41.3 dB/m vs. 269.3 ± 79.7 dB/m; $p=0.156$). Also, no significant difference was found for the median of CAP values between patients with and without liver steatosis on ultrasound (198 [144-262] dB/m vs. 191 [169-364] dB/m; $p=0.892$) (Figure 2).

Figure 2 Median values of the controlled attenuation parameter (CAP) between patients without (n=17) and with suggestive of significant fibrosis (n=4). *Significance level by Student's t-test (a). Median CAP values between patients without (n=7) and with ultrasound liver steatosis (n=11). *Significance level of the Mann-Whitney U test (b).

In calculating the accuracy of values equal to or greater than twice the upper limit of normal for AST and ALT enzymes as predictors of significant liver fibrosis, a sensitivity of 80% (CI95% 28.4-99.5) and specificity of 95% (CI95% 75.1-99.9), which suggests that the increased values of these enzymes may contribute to the screening of liver fibrosis in these patients.

Discussion

The present study showed that 20% of the A-T patients evaluated presented a suggestive diagnosis of significant liver fibrosis. It is important to emphasize that all the patients with suggestive of liver fibrosis had dyslipidemia and four had diabetes. The presence of suggestive diagnosis of fibrosis was associated with the severity of ataxia and with higher values of liver enzymes, ferritin, 120-minutes glycemia by OGTT and the HOMA-AD and lower values for the Matsuda index, compared to A-T patients without liver fibrosis.

Regarding the liver biomarkers evaluated, only liver enzymes (ALT, AST and GGT) were elevated in patients with a suggestive diagnosis of significant liver fibrosis. Values equal to or greater than twice the upper limit of normal for AST and ALT enzymes as predictors of significant liver fibrosis revealed a sensitivity of 80% and a specificity of 95%. In a previous study performed by our group, the values of the ALT and AST have shown alterations mainly during adolescence in A-T patients [5]. In a retrospective study with A-T patients conducted by Donath et al. a steady upward evolution of ALT and GGT was observed, especially from the age of 12 [9]. In another retrospective study, elevation of liver enzymes was observed in younger A-T patients with a mean age of 9.97 ± 5.09 years and a significant association with the presence of dyslipidemia [10]. Therefore, it is recommended periodic monitoring of the AST and ALT liver enzymes from the age of 10, which may contribute to the screening of liver fibrosis in A-T patients

In the present study, patients diagnosed with diabetes had fasting glucose within the normal range and were only identified by OGTT with 120-minutes glycemia above 200 mg/dL. The findings suggest the importance of performing the OGTT for early identification and treatment of diabetes, especially from adolescence. A cohort of A-T patients showed a progressive increase in glycated hemoglobin (HbA1c) and fasting glucose with advancing age. OGTT was considered to have good sensitivity for IR screening and the HbA1c a marker to assess the therapy response [53].

Regarding the indices used to assess IR, the values of the HOMA-AD and Matsuda differed significantly between patients with and without a suggestive diagnosis of significant liver fibrosis; fact not observed for HOMA-IR. A controlled study has also verified lower values of Matsuda index in A-T patients compared to healthy individuals (5.96 ± 0.77 vs. 11.03 ± 1.69 ; $p=0.019$) and similar values of HOMA-IR between the groups [54]. A recent study conducted with Brazilian children and adolescents for metabolic

syndrome screening has found a better performance of HOMA-AD compared to HOMA-IR [46]. Furthermore, Hung et al. observed that HOMA-AD appears to be sensitive in detecting small changes in insulin sensitivity in patients with or without diabetes [55]. Therefore, to assess IR in A-T patients by HOMA-IR seems not to be the most appropriate method.

Regarding inflammatory biomarkers, only ferritin had higher values in patients with suggestive of liver fibrosis compared to those who did not. Experimental study with the aim of investigating the iron regulation, regulatory genes, and markers of oxidative stress in the liver tissue of ATM-deficiency mice, described higher values of serum and hepatic iron, ferritin, and hepcidin when compared to controls. This study suggested that the increase in tissue iron would be associated with hepatic oxidative stress resulting from iron-induced increase in hepcidin, which can suppress its export by ferroportin, which is considered a protective mechanism in response to oxidative stress [56]. Therefore, it is suggested that the increase in ferritin may contribute to the chronic oxidative stress presented by A-T patients and, consequently, to the development of liver disease.

Another noteworthy fact was the significant and direct correlation between the median LSM obtained by TE and the ICARS score. In a retrospective study aiming to determine the evolution of liver disease and its relationship with age and neurological impairment in A-T patients, a significant and direct correlation was found of the Klockgether Ataxia Scale (KAS) score with age, AFP, GGT, and ALT [9]. In a recent study conducted by our group, correlations were found between the severity of ataxia with age and metabolic changes including impairment of liver damage markers and IR in A-T patients [57].

Regarding the CAP values obtained by TE, no significant difference was observed between patients with and without suggestive diagnosis of significant fibrosis. By ultrasound, three of the five patients with suggestive of liver fibrosis presented steatosis. Therefore, only the presence of hepatic steatosis by both ultrasound and CAP was not related to hepatic fibrosis in A-T patients, which suggests that the presence of steatosis is not a predictive factor for fibrosis in these patients.

One of the mechanisms of ATM protein activation is attributed to the action of reactive oxygen species (ROS), resulting in increased concentrations of antioxidants and the repair of oxidative DNA damage. In the absence/deficiency of ATM, A-T patients have low antioxidant capacity and as a result macromolecules, lipids and DNA are exposed to constant oxidative stress and its damages [58–60]. NAFLD and A-T share a similar pathogenic mechanism of ROS generation and mitochondrial dysfunction that contributes to the development of lesions [61]. Thus, it is postulated that oxidative stress has a relevant contribution in the genesis of liver disease associated with A-T.

The mechanisms involved in the evolution of NAFLD are not fully known. Changes in proteins such as ATM could play a role in these mechanisms since this protein is associated with DNA integrity and mitochondrial homeostasis. An experimental study showed that ATM-deficient mice presented a reduction and delay in DNA replication during liver regeneration. Furthermore, when partial hepatectomy was performed, an increase in apoptosis was observed, which indicates that the ATM protein is involved in the regeneration and survival of hepatocytes [62].

A recent study that analyzed the expression of messenger RNAs, total proteins, or phosphoproteins related to the ATM pathway of individuals with healthy liver, hepatic steatosis, and NASH, found a causal association between the ATM pathway and NAFLD. During the steatosis phase, there was low ATM activation, which caused mitochondrial dysregulation and greater DNA damage, in addition to reduced growth of the hepatocyte. In NASH, there was greater ATM depletion, with a greater degree of DNA damage and cell growth arrest due to the action of ATM in the cell cycle. In addition, to compensate for hepatocyte growth arrest, pre-oncogenic cells appeared, with a high rate of proliferation [63]. Therefore, the ATM protein appears to play an important role both in the beginning and progression of NAFLD, including its evolution to HCC.

This study has as strengths the fact that it is unprecedented in the sense of describing a suggestive diagnosis of liver fibrosis in A-T patients through non-invasive methods and prospective data collection. As limitations, we can consider the absence of genotyping of the *ATM* gene variants and the small number of patients with suggestive of liver fibrosis, which limited the analysis.

Conclusions

Suggestive findings of significant liver fibrosis by non-invasive markers were observed in 20% of A-T patients. The presence of fibrosis was associated with alterations in liver enzymes, ferritin, increase in the HOMA-AD, and severity of ataxia. The findings lead to the importance of monitoring liver and metabolic changes through non-invasive imaging and laboratory methods, especially from adolescence.

Abbreviations

ALT – Alanine aminotransferase

ALKP - alkaline phosphatase

APRI - AST to platelet ratio index

AST – Aspartate aminotransferase

A-T – Ataxia-telangiectasia

ATM – Ataxia telangiectasia mutated

BMI – Body mass index

CAP - controlled attenuation parameter

CK-18 - cytokeratin-18

MUAC - mid-upper arm circumference

TC – total cholesterol

ELISA - Enzyme Linked Immunosorbent Assay

ESID - European Society for Immunodeficiencies

GGT - Gamma glutamyl transferase

HbA1c - glycated hemoglobin

HCC - hepatocellular carcinoma

HDL-c - high density lipoprotein cholesterol

HOMA-AD - Homeostasis Model Assessment - Adiponectin

HOMA-IR - Homeostasis Model Assessment - Insulin Resistance

hs-CRP - High-sensitivity C-reactive protein

ICARS - International Cooperative Ataxia Rating Scale

IQR - interquartile range

IR - insulin resistance

IVIg - intravenous immunoglobulin

LDL- c - low density lipoprotein cholesterol

LMS - liver stiffness measurement

kPa - kilopascals

KAS - Klockgether ataxia score

NAFLD - Nonalcoholic fatty liver disease

NASH - Nonalcoholic steatohepatitis

NCEP - National Cholesterol Education Program

NFS - Nonalcoholic Fatty Liver Disease Fibrosis Score

NHDL-c - non-HDL-c

OGTT - oral glucose tolerance test

rho - correlation coefficient

ROS – reactive oxygen species

SAA - serum amyloid A

SR - success rate

TE - Transient elastography

TG - triglycerides

TNF- α - tumor necrosis factor alpha

WC - waist circumference

WHtR – waist circumference to height ratio

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee in Research of the Universidade Federal de São Paulo (UNIFESP), identification number 0081/2018.

Consent for publication

Patients and parents gave consent to be included in the study through consent form.

Availability of data and material

All data generated or analysis during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TLNB: Acquisition of data, drafting of the manuscript, statistical analysis, and interpretation of data of the manuscript.

RJCF: Carried out image exams, statistical analysis, study supervision, and critical revision for important intellectual content.

DCS: Carried out image exams, study supervision, and critical revision for important intellectual content.

FLAF: Carried out the biochemical analysis.

ACF: Carried out the biochemical analysis.

CK: Study supervision and critical revision for important intellectual content.

CSA: Study supervision and critical revision for important intellectual content.

ROSS: Concept and design development; drafting of the manuscript; study supervision and critical revision for important intellectual content.

All authors read and approved the final manuscript.

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Tables

Table 1
Characteristics of the patients with Ataxia-telangiectasia

Variables		N (%)
Age (n=25)	Children (<10 years)	9 (36.0%)
	Adolescents (10 to 19 years)	11 (44.0%)
	Adults ($\geq$ 20 years)	5 (20.0%)
Nutritional status (n=25)	Malnutrition	8 (32.0%)
	Eutrophy	16 (64.0%)
	Overweight	1 (4.0%)
Fat mass (n=24)	Low	4 (16.7%)
	Adequate	13 (54.1%)
	High	7 (29.1%)
MUAMC (n=24)	Low	13 (54.1%)
	Adequate	11 (45.8%)
WHtR (n=24)	Adequate	20 (83.3%)
	High	4 (16.7%)
Pubertal stage (n=25)	Prepubescent	9 (36.0%)
	Pubescent	8 (32.0%)
	Postpubescent	8 (32.0%)
ICARS (n=25)	Mild ataxia	3 (12.0%)
	Moderate ataxia	13 (52.0%)
	Severe ataxia	9 (36.0%)
hs-CRP (n=25)	>1mg/L	7 (28.0%)
	$\leq$ 1mg/L	18 (72.0%)
Lipid profile (n=25)	High total cholesterol	5 (20.0%)
	High LDL-c	5 (20.0%)
	High triglycerides	6 (24.0%)

N (%): absolute and percentage values. Abbreviations: MUAMC (mid-upper arm muscle circumference), WHtR (waist circumference/height ratio), hs-CRP (high sensitivity C reactive protein), ICARS (International Cooperative Ataxia Rating Scale), HOMA-AD (Homeostasis Model Assessment-Adiponectin), ALT (alanine aminotransferase), AST (aspartate aminotransferase), xULN (times the upper limit of normal).

Variables		N (%)
Diabetes	Low HDL-c	8 (32.0%)
	High NHDL-c	14 (56.0%)
		4 (18.2%)
(n=22)		
HOMA-AD	Insulin resistance	5 (29.4%)
(n=17)	Absent	7 (35.0%)
Hepatic steatosis		
(n=20)	Mild	8 (40.0%)
	Moderate	5 (25.0%)
Significant liver fibrosis		5 (20.0%)
(n=25)		
ALT (U/L)	≥ 2 xULN	4 (16.0%)
(n=25)		
AST (U/L)	≥ 2 xULN	2 (8.0%)
(n=25)		
N (%): absolute and percentage values. Abbreviations: MUAMC (mid-upper arm muscle circumference), WHtR (waist circumference/height ratio), hs-CRP (high sensitivity C reactive protein), ICARS (International Cooperative Ataxia Rating Scale), HOMA-AD (Homeostasis Model Assessment-Adiponectin), ALT (alanine aminotransferase), AST (aspartate aminotransferase), xULN (times the upper limit of normal).		

Table 2. Values of the parameters of the transient elastography and liver fibrosis scores in patients with suggestive diagnosis of significant liver fibrosis

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5*
Age (years)	20	29	31	27	29
Median CAP (dB/m)	364	198	306	209	
CAP IQR (dB/m)	28	97	30	38	
Median LSM (kPa)	8.9	38	8.7	11.8	
LSM IQR (kPa)	2.6	5.1	1.1	1.2	
LSM IQR/Md (%)	29	13	13	10	
Success Rate (%)	100	100	100	65	
Valid measurements	11	14	10	11	
APRI	0.57	0.93	0.58	0.72	0.70
NFS	-2.047	0.975	-1.463	-0.502	-0.557
BARD score (points)	2	3	1	0	3

Abbreviations: CAP (controlled attenuation parameter), IQR (interquartile range), LSM (liver stiffness measurement), IQR/Md (interquartile range to median measurements ratio), APRI (aspartate aminotransferase to platelet ratio index) and NFS (nonalcoholic fatty liver disease fibrosis score).

*Transient elastography was not performed in patient 5.

Table 3. Comparison of the patients with Ataxia-telangiectasia according to the presence or absence of a suggestive of significant liver fibrosis

Variables		Absence of significant fibrosis (n=20)	Suggestive of significant fibrosis (n=5)	P- value ^{a,b}
Age	years	11.1 ± 4.2 ^c	27.2 ± 4.3	<0.001 ^a
BMI	Kg/m ²	14.8 (11.8-26.8)	20.8 (10.6-24.1)	0.118 ^b
Fat mass	%	17.9 ± 7.6	20.4 ± 5.4	0.553 ^a
MUAMC	mm	169.8 ± 42.8	240.8 ± 6.9	<0.001 ^a
WC	cm	54.5 (47.0-90.0)	78.0 (68.0-82.0)	0.008 ^b
WHtR		0.44 ± 0.06	0.49 ± 0.03	0.098 ^a
ICARS	points	49.7 ± 20.1	76.0 ± 7.7	0.009 ^a
Platelets	10 ³ /mm ³	382 ± 100.5	266 ± 85.5	0.027 ^a
Albumin	g/dL	4.5 ± 0.3	4.0 ± 0.7	0.019 ^a
TC	mg/dL	167.9 (119.7-247.0) ^d	180.1 (172.4-289.5)	0.154 ^b
LDL-c	mg/dL	101.7 (69.0-179.2)	130.0 (102.4-198.9)	0.049 ^b
HDL-c	mg/dL	47,3 ± 12,6	30.9 ± 10.1	0.013 ^a
TG	mg/dL	77.1 (35.0-196.7)	110.4 (53.4-331.0)	0.103 ^b

NHDL-c	mg/dL	115.5 (76.0-189.0)	152.1 (131.0-265.1)	0.067 ^b
AST	U/L	29.9 (16.6-74.3)	75.5 (46.9-82.3)	0.001^b
ALT	U/L	20.7 (11.4-73.4)	89.4 (32.3-144.5)	0.002^b
GGT	U/L	26.0 (7.0-102.0)	259.0 (108.0-612.0)	0.001^b
ALKP	U/L	230.5 (113.0-497.2)	176.7 (111.2-355.0)	0.684 ^b
CK-18	mIU/mL	252.8 (39.2-741.1)	191.4 (21.4-333.8)	0.374 ^b
AFP	UL/mL	281.9 ± 177.8	240.4 ± 133.9	0.632 ^a
Ferritin	ng/mL	82.3 (29.0-256.0)	419.0 (303.0-1538.0)	0.001^b
hs-CRP	mg/L	1.0 (0.39-9.8)	2.2 (0.20-53.1)	0.424 ^b
TNF-alpha	pg/mL	139.8 ± 8.5	142.0 ± 14.9	0.768 ^a
Adiponectin	µg/mL	7.0 ± 3.9	3.5 ± 2.9	0.084 ^a
SAA	ng/mL	11.3 (9.0-147.2)	20.4 (9.0-73.7)	0.111 ^b
Fasting glucose	mg/dL	85.7 ± 9.3	90.7 ± 17.9	0.628 ^a

120-min glycemia	mg/dL	90.2 ± 22.3	224.5 ± 84.8	0.049^a
HOMA-IR		1.4 (0.08-4.5)	6.9 (1.4-20.9)	0.060 ^b
HOMA-AD		4.1 (0.25-110.0)	108.1 (6.9-213.9)	0.016^b
Matsuda index		9.2 (1.5-81.3)	3.3 (0,6-4.5)	0.044^b

^a Significance Level of independent Student t-test

^b Significance Level of the Mann-Whitney U test.

^c Mean (standard deviation)

^d Median (minimum – maximum)

Abbreviations: BMI (body mass index), MUAMC (mid-upper arm muscle circumference), WC (waist circumference) International Cooperative Ataxia Rating Scale (ICARS), TC (total cholesterol), HDL-c (cholesterol high density lipoprotein), LDL-c (cholesterol low density lipoprotein), TG (triglycerides), NHDL-c (non-HDL-c), ALT (alanine aminotransferase), AST (aspartate (aminotransferase), GGT (gama-glutamyl transferase), ALKP (alkaline phosphatase), CK-18 (cytokeratin-18), AFP (alpha-fetoprotein), hs-CRP (high sensitivity C reactive protein), TNF-alpha (tumor necrosis factor alpha), SAA (serum amyloid A protein), min. (minutes), HOMA-IR (Homeostasis Model Assessment - Insulin Resistance) and HOMA-AD (Homeostasis Model Assessment - Adiponectin).

Figures

Figure 1

Scatter plot for the correlation of the liver stiffness measurement (LSM) values with the HOMA-AD (Homeostasis Model Assessment – Adiponectin) (a), nonalcoholic fatty liver disease fibrosis score (NFS) (b), and International Cooperative Ataxia Rating Scale (ICARS) (c). (n=21). *Significance level of the Spearman correlation coefficient. Cut-off point ≥ 7 kPa adopted for the liver fibrosis (dotted line).

Figure 2

Median values of the controlled attenuation parameter (CAP) between patients without (n=17) and with suggestive of significant fibrosis (n=4). *Significance level by Student's t-test (a). Median CAP values between patients without (n=7) and with ultrasound liver steatosis (n=11). *Significance level of the Mann-Whitney U test (b).

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