Digestive and Liver Disease 51 (2019) 1599–1603

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Liver stiffness assessment by transient elastography suggests high prevalence of liver involvement in common variable immunodeficiency

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ARTICLE INFO

Article history:
Received 29 January 2019
Accepted 9 May 2019
Available online 31 May 2019

Keywords:
Antibody deficiency
Fibroscan
Primary immunodeficiency

ABSTRACT

Background: Up to 50% of patients with common variable immunodeficiency (CVID) present persistently increased serum levels of liver enzymes and/or mild hepatomegaly. Ultrasound-based transient elastography (TE) is largely used for early detection of the progression of chronic liver diseases, but has never been employed in CVID. We performed a cross-sectional study to evaluate TE values in a cohort of adult CVID-patients.
Methods: Full blood count, liver function test, liver and spleen sonogram and ultrasound-based TE were performed in 77 adult CVID patients. Demographic and clinical data were retrospectively collected from medical files.
Results: 33.8% (26/77) patients presented increased TE values ranging from moderate fibrosis to cirrhosis. TE values were positively correlated with ALP, γGT, spleen longitudinal diameter and peripheral blood counts (no significant correlation with BMI, AST, ALT, total proteins, albumin, bilirubin and hemoglobin). Moreover, liver stiffness was higher in patients with the clinical phenotypes polyclonal lymphoproliferation and enteropathy, and patients with both these complications had an increased risk (OR: 7.14) of presenting pathologic TE values compared with those without anyone of these.
Conclusions: Transient elastography is a useful tool to be used alongside clinical and laboratory data to assess liver involvement in CVID.

1. Introduction

Common variable immunodeficiency (CVID), the most frequent symptomatic primary antibody deficiency in adulthood, is characterized by reduced serum levels of IgG, IgA, and/or IgM and impaired antibody production in response to pathogens [1]. CVID has complex pathogenetic mechanisms arising either from an intrinsic defect in B cell differentiation or from an impaired cross-talk between B and T cells [2–4].

The heterogeneity of CVID is mirrored by the wide spectrum of clinical manifestations: while most patients experience only recurrent bacterial infections, a subset are additionally affected by various manifestations of immune dysregulation including autoimmunity, granulomatous disease with lymphoid hyperplasia (defined as polyclonal lymphoproliferation), and malignancies [5,6]. These non-infectious complications also involve various segments of the gastrointestinal tract leading to life-threatening complications as protein-energy malnutrition, malabsorption and gut microbial translocation [7,8].

Up to 50% of CVID patients present persistently increased serum levels of liver enzymes (mainly alkaline phosphatase - ALP) associated with mild hepatomegaly [9]. The most commonly identified cause of liver impairment in CVID is nodular regenerative hyperplasia (NRH) that is thought to be related to an intrahepatic vasculopathy causing hepatocyte injury and regeneration. This results in the formation of characteristic nodules with subsequent compression of hepatic parenchyma and blood vessels [10,11]. In addition to NRH, viral infections, granulomatous disease, intrahepatic biliary obstruction, lymphoproliferation and malignancies have been reported as contributors of liver involvement in CVID [12].

Although liver biopsy with immunohistochemical analysis represents the gold standard to ascertain liver damage, it is associated

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https://doi.org/10.1016/j.dld.2019.05.016
1590-8658/

with an estimated morbidity and mortality rate in general population of 3% and 0.01%, respectively [13]. In the context of CVID, liver biopsy may be burdened by an additional infectious risk due to the underlying immune defect. Moreover, the frequent presence of severe thrombocytopenia, makes liver biopsy dangerous to be carried out routinely. Therefore, the screening work-up of liver involvement in CVID is generally limited to laboratory tests and color Doppler ultrasound evaluation.

In last years, ultrasound-based transient elastography (TE) has been largely employed and validated for early detection of the progression of chronic liver diseases (namely chronic hepatitis C) [14]. The measurement of liver stiffness by TE depends on a vibration-generating machine to apply vibrations to the liver and then obtain the propagation velocity of shear wave [15]. We read with interest the article by Meijer et al. published on this journal on the use of TE to assess liver stiffness in patients with inflammatory bowel disease (IBD) [16]. In that study, the authors assessed the prevalence of liver fibrosis in a cohort of IBD patients by the use of TE and highlighted a trend towards lower liver stiffness in patients using thiopurines. Moreover, they found that liver stiffness correlated positively with liver enzyme tests and negatively with platelet count.

Similarly, here we present the results of a cross-sectional monocentric study assessing: (a) the prevalence of liver involvement in a cohort of adult CVID-patients by the use of ultrasound-based TE; (b) the correlation between TE values and the major clinical markers of liver involvement (i.e., liver enzymes, peripheral blood counts and longitudinal spleen diameter); (c) the association between liver stiffness values and the presence of specific clinical phenotypes of CVID.

2. Methods

2.1. Recruitment of subjects

Seventy-seven CVID adult patients (37 males; mean age 44.7 ± 14.4 years) were enrolled in the study from June 2018 to March 2019 at the Centre of Primary Immunodeficiency of the Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy. CVID diagnosis was based on the 2014 ESID diagnostic criteria [17]. All the enrolled patients were on chronic immunoglobulin replacement therapy, the mainstay of therapy to reduce the incidence and the severity of recurrent infections [18–20], via either the intravenous or the subcutaneous route. Subjects with acute or chronic viral hepatitis were excluded from the study. None of the patients suffered from opportunistic infections typical for late-onset combined immunodeficiency. There were three familial cases in the cohort, but no monogenic form of CVID was detected through whole exome sequencing. All the participants in the study were Caucasians. From the medical files, we retrospectively collected age at diagnosis, clinical history of recurrent infections, autoimmune disorders (autoimmune hemolytic anemia, thrombocytopenia and neutropenia), polyclonal lymphoproliferation (splenomegaly, lymphadenopathy, and granulomatous disease), enteropathy (chronic diarrhea, celiac-like enteropathy, inflammatory bowel diseases) and malignancies. Written informed consent was obtained from all participants at the time of inclusion in the study. All the research procedures were conducted in accordance with the principles of the Helsinki II Declaration.

2.2. Study procedures

Enrolled subjects underwent peripheral blood sampling for hematological parameters (including blood count, AST, ALT, ALP, γGT, bilirubin, total proteins, albumin, serum IgG pre-infusional levels), liver and spleen sonographic evaluation and ultrasound-based TE. All the procedures were performed at least eight hours after food intake. Liver stiffness measurements were performed, as previously described [12], by a scanning procedure-trained practitioner (AF) and supervised by a specialist hepatologist (AR). Scoring and cut-off TE values for liver disease were derived from a large population study including patients with various etiologies of chronic liver disease [11]: F0/F1 — absent to mild fibrosis: <7.3 kPa; F2 — moderate fibrosis: 7.3–12.5 kPa; F3 — severe fibrosis: 12.6–17.6 kPa; F4 — cirrhosis: >17.6 kPa.

2.3. Statistical analysis

Data are expressed as means ± standard deviation of the mean. Comparative analysis was performed using parametric unpaired t-test for continuous variables with normal distribution. Correlations were assessed using parametric Pearson's test. Comparison of multiple data sets was performed using one-way ANOVA followed by the Dunn multiple correction test. Statistical analysis defining association between clinical phenotypes and high TE values was conducted using a Fisher's exact test. Confidence interval of the odds ratio was computed using the Baptista-Pike method. Results were analyzed with GraphPad Prism software (version 8.02; GraphPad Software, La Jolla, Calif). P values were two-sided and considered significant when <0.05.

3. Results

3.1. Liver stiffness values

Clinical and demographic characteristics of patients are summarized in Table 1. Mean age at the diagnosis of CVID was 36.5 ± 15.2 years, while the age of onset of immunodeficiency-related symptoms was 28.2 ± 12.2 years. Liver stiffness measurements assessed by TE ranged from 2.7 to 34.8 kPa with a mean value of 7.5 kPa (SD ± 4.6). Fifty-one patients (66.2%) had absent or mild fibrosis (F0/F1), 18 patients (23.4%) displayed a moderate fibrosis (F2) and 6 patients (7.8%) had severe fibrosis (F3). Two patients had liver cirrhosis (F4). One patients was a 46 year-old man with a history of large B-cell non-Hodgkin lymphoma and severe granulomatous lymphocytic interstitial lung disease (GLILD), with a liver stiffness value of 34.8 kPA. The other one was a 20 year-old man with diffuse non-malignant lymphoadenopathy and a liver stiffness value of 18 kPA. Among the 26 patients with increased liver stiffness values,

Table 1
Demographic and clinical characteristics of the cohort.

	Study population (n = 77)
Gender, n (%)	
Male	37 (48)
Age (years), mean ± SD	44.7 ± 14.4
BMI (kg/m^2), mean ± SD	24.1 ± 4.7
Age at CVID symptoms onset (years), mean ± SD	28.2 ± 12.2
Age at CVID diagnosis (years), mean ± SD	36.5 ± 15.2
Clinical phenotype[a], n (%)	
Infections only	20 (25.9)
Autoimmune cytopenias	16 (20.7)
Polyclonal lymphoproliferation	36 (46.7)
Enteropathy	28 (36.3)
Malignancies	6 (7.7)
Fibrosis score, n (%)	
F0/F1: no to mild fibrosis	51 (66.2)
F2: moderate fibrosis	18 (23.4)
F3: severe fibrosis	6 (7.8)
F4: cirrhosis	2 (2.6)

[a] Excluding "infections only", clinical phenotypes are not mutually exclusive. SD: standard deviation; BMI: body mass index; CVID: common variable immunodeficiency.

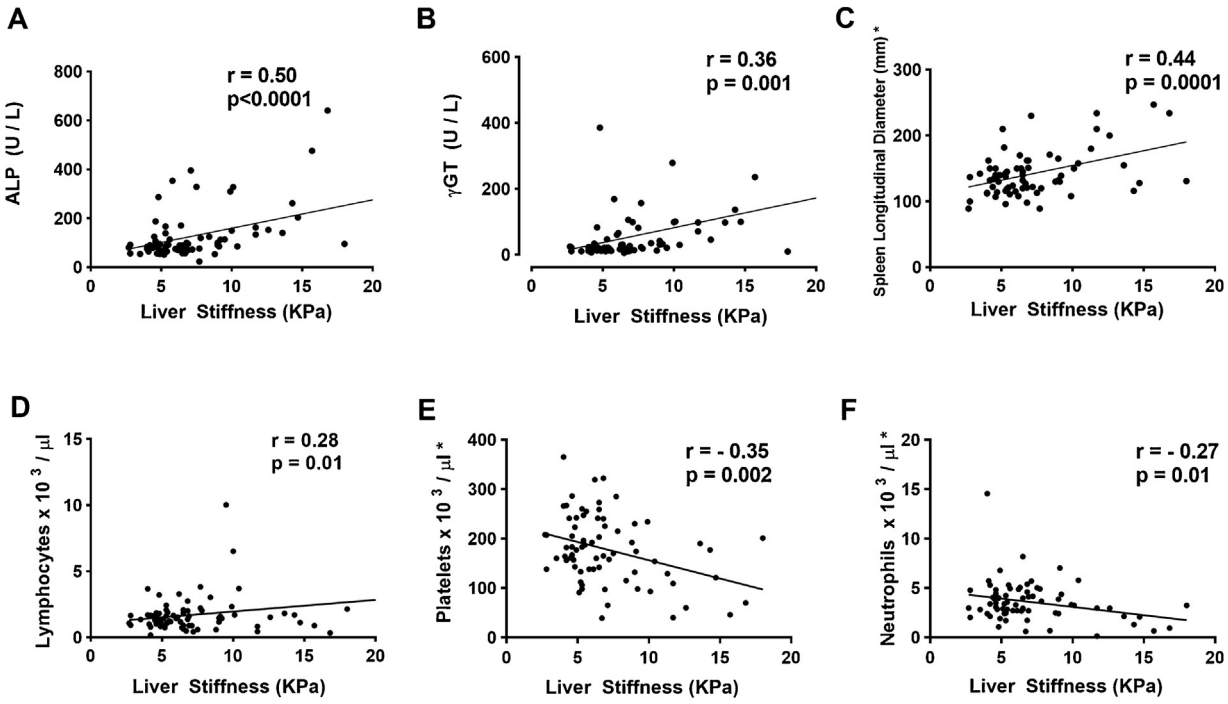

Fig. 1. Correlation between liver stiffness measured by ultrasound-based transient elastography and (A) ALP, (B) γGT, (C) spleen longitudinal diameter, (D) lymphocyte, (E) platelet and (F) neutrophil count in a cohort of 77 CVID adult patients (Pearson's test). *Splenectomized patients were excluded by the analysis showed in (C), (E) and (F). N.B.: To enhance graphical representation, one subject with a liver stiffness value of 34 kPa was excluded by the figure but not from the statistical analysis.

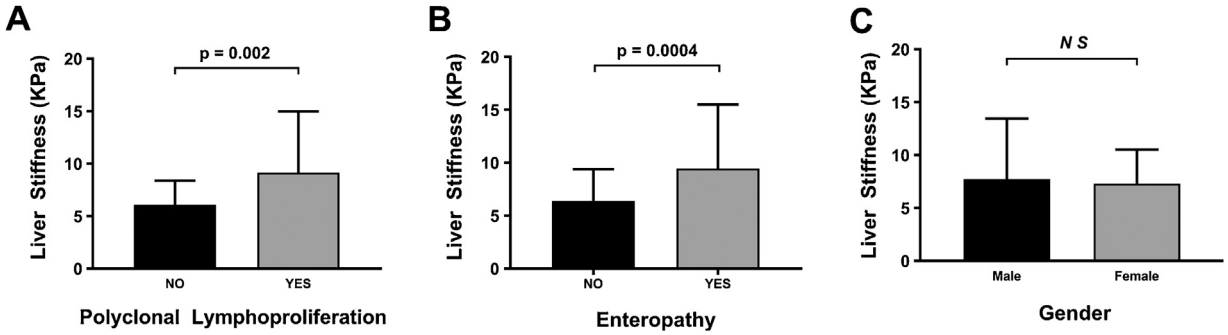

Fig. 2. Liver stiffness values in a cohort of 77 CVID adult patients stratified according to the clinical phenotypes polyclonal lymphoproliferation (A) and enteropathy (B), and the gender (C) (unpaired t-test).

mild hepatomegaly (16/26) and coarsened parenchymal echotexture (5/26) were the major sonographic findings.

3.2. Correlation with clinical markers of liver involvement

Liver stiffness was positively correlated with serum levels of ALP ($r = 0.50$, $p < 0.0001$), γGT ($r = 0.36$, $p = 0.001$), spleen longitudinal diameter ($r = 0.44$, p 0.0001) and peripheral count of blood lymphocytes ($r = 0.28$, $p = 0.01$) (Fig.1 A–D). No significant correlation was found between TE values and body mass index, AST, ALT, total proteins, albumin, bilirubin and hemoglobin (data not shown). Although there was a trend between higher liver stiffness values and lower platelet ($r = -0.2$; $p = 0.12$) and neutrophil ($r = -0.21$; $p = 0.06$) counts, this did not reach statistical significance. We argued that the lack of significant correlation was because splenectomized subjects (5 patients), who presented high TE values, had also high platelet and neutrophil counts values as consequence of splenectomy-related hemocatheretic changes. Therefore, when we excluded splenectomized subjects from the analysis, a negative correlation between liver stiffness and both platelet ($r = -0.35$, $p = 0.002$) and neutrophil ($r = -0.27$, $p = 0.01$) count was found (Fig. 1E and F).

3.3. Association with the clinical phenotypes of CVID

Thirty-six of 77 (46.7%) patients presented the clinical phenotype "polyclonal lymphoproliferation" (defined as the presence of granulomatous infiltrates and/or interstitial lymphocytic pneumonia and/or persistent unexplained lymphadenopathy with or without hepatosplenomegaly), while 28/77 (36.3%) had the clinical phenotype "enteropathy" (defined as the histopathological finding of lymphocytic infiltrates in small or large bowel associated with chronic non-infectious diarrhea). Liver stiffness was higher in the subsets of patients with polyclonal lymphoproliferation ($p = 0.002$; Fig. 2A) and enteropathy ($p = 0.0004$: Fig. 2B). No differences in TE measurements were found between males and females ($p = 0.64$; Fig. 2C). Excluding the "infections only phenotype", clinical phenotypes of CVID are not mutually exclusive and 17 patients in our cohort had both polyclonal lymphoproliferation and enteropathy (E + PL+). Interestingly, this latter subset presented the

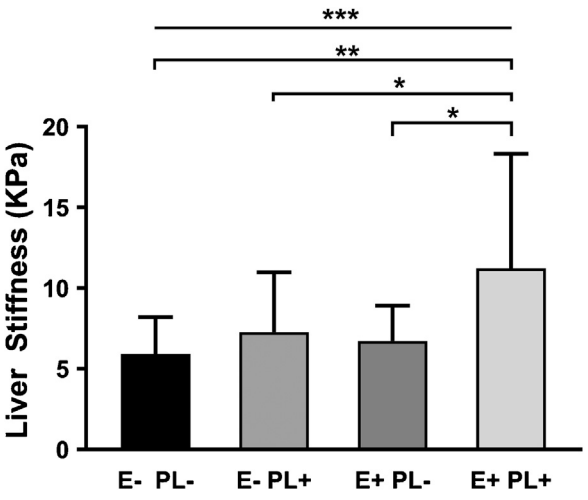

Fig. 3. Liver stiffness values in a cohort of 77 CVID adult patients stratified according to the presence of: neither polyclonal lymphoproliferation nor enteropathy (E− PL−), only polyclonal lymphoproliferation (E− PL+), only enteropathy (E + PL−), both polyclonal lymphoproliferation and enteropathy (E + PL+). * = $p < 0.05$; ** = $p < 0.01$. (One-way ANOVA followed by the Dunn multiple correction test).

highest liver stiffness values when compared not only with patients without anyone of these two phenotypes (E − PL−), but also with patients with only polyclonal lymphoproliferation (E − PL+) and only enteropathy (E + PL−) (Fig. 3). Patients with both polyclonal lymphoproliferation and enteropathy (PL + E+) had an increased risk (OR: 7.14; 95% CI: 1.89 to 28.96; $p = 0.007$) of presenting pathologic TE values (ranging from moderate fibrosis to cirrhosis; F2–F4: >7.3 kPa) compared with those without anyone of these complications (PL − E−). These findings confirm the hypothesis that liver involvement in CVID is related to the typical immune dysregulation of the disease.

4. Discussion

In our cohort of 77 CVID adult patients, a high percentage (33.8%) of subjects presented increased TE values ranging from moderate fibrosis to cirrhosis (F2–F4). This observation supports the hypothesis that liver disease is a frequent and underdiagnosed complication of CVID that may significantly affect long-term outcome. The prevalence of liver involvement in CVID was first described in 1999 in a 248 subjects' cohort, where clinical, laboratory and histological signs of liver damage were present in 11.9% of patients [21]. A 2008 study pinpointed cholestasis (65%), portal hypertension (50%) and elevated transaminases (49%), as the main hepatic manifestations in a 51 patient's cohort [22]. Similarly, Ward et al. found deranged liver function, mostly consisting in raised alkaline phosphatase levels, in 43.5% (47/108) patients [9]. Most recent studies report a clinically- and histologically-proved prevalence of liver disease in CVID of 9.1–9.3% [24,25]. Furthermore, Resnick et al. found that the risk of death was 2.48 times higher for CVID patients with liver disease compared to patients without this complication [23]. Although all these studies had highlighted liver disease as a common complication of CVID, no diagnostic algorithm has been proposed or evaluated. However, laboratory (i.e., AST, ALT, ALP, GGT, bilirubin), radiological (i.e., ultrasound scan, magnetic resonance) and histological (i.e., liver biopsy with immune-histochemistry) tools are currently used in clinical practice to ascertain the cause of deranged liver function in CVID patients.

To the best of our knowledge, this is the first study that evaluates the use of transient elastography to assess liver involvement in CVID. The linear correlations between liver stiffness values and various direct (ALP, γGT, spleen longitudinal diameter) and indirect (lymphocytes, platelets and neutrophils) markers of liver disease support the potential utility of transient elastography to estimate the prevalence of liver involvement in CVID. The correlation between TE values and ALP is of particular interest, since this latter had been already pinpointed as the main laboratory marker associated with NRH that represents the most frequently identified cause of liver disease in CVID [9,10,22]. In particular, Ward et al. identified 3 different patterns of ALP derangement including progressive elevation, fluctuating increase and transient increase only [9]. In this perspective, it would be interesting to investigate in future studies how intra-individual variations of TE values over time are associated with the trends of ALP serum levels.

In our cohort, liver stiffness was higher in CVID patients with the clinical phenotypes "polyclonal lymphoproliferation" and "enteropathy" (Fig.2), and the highest TE values were found in patients presenting both these complications (Fig.3). As mentioned above, polyclonal lymphoproliferation is characterized by the presence of granulomatous infiltrates, interstitial lymphocytic pneumonia and persistent unexplained lymphadenopathy, frequently associated with splenomegaly [5]. Different factors could contribute to derange liver function in CVID patients with polyclonal lymphoproliferation: one hypothesis is that the increase of blood flow from the enlarged spleen may cause an increase of blood pressure in portal vein system leading to an intrahepatic vasculopathy [25]. Alternatively, or in addition to this, granulomatous infiltrates may develop in liver parenchyma, as a secondary lymphoid organ, thus deranging directly liver stiffness. In this regard, Malamut et al. found small lobular, non-necrotizing, non-fibrosing granulomata in 10/23 (43.5%) liver biopsies from CVID patients with deranged liver function [22], while a lower prevalence of granulomatous inflammation (14% and 23%) was observed in two similar histopathological studies [9,10].

The enteropathy associated with CVID is characterized by chronic diarrhea associated with the finding of inflammatory infiltrates in small or large bowel resembling the pathological changes observed in celiac disease or in inflammatory bowel diseases, in general population. One hypothesis to explain the association between liver involvement and CVID-related enteropathy is that bowel inflammation may derange intestinal permeability thus affecting metabolic and immune responses in liver. Accordingly with our findings, Ward et al. found a significant association ($p < 0.0001$) between the histological finding of NRH and the clinical phenotype enteropathy in a cohort of 108 CVID patients [9]. Future studies assessing the correlation between the impairment of intestinal permeability and the increase of liver stiffness will be needed to evaluate the real impact of this possible mechanism.

5. Conclusions

Although in our cohort TE values were associated with both laboratory abnormalities and clinical phenotype, neither liver stiffness assessment nor liver function tests are able to ascertain the etiopathogenetic nature of liver involvement. Morphological and immunohistochemical evaluation of liver biopsy are probably essential to both uncover the pathogenesis of liver involvement and offer personalized therapeutic options to these patients. Therefore, we suggest that transient elastography could be used, alongside clinical and laboratory data, to select patients eligible for an invasive second-level test such as liver biopsy.

Further studies, evaluating the concordance between stiffness values and liver histopathological findings, are required to precisely assess the role of elastography in the evaluation and management of liver involvement in larger cohorts of CVID patients.

Conflict of interest
None declared.

Source of support

Departmental Funds.

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