Association of KL-6 Levels with Interstitial Lung Disease in Connective Tissue Diseased Children, case control study

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November 2, 2020

Abstract

It was aimed to evaluate the correlation between serum KL-6 levels with both presence of interstitial lung disease (ILD) and its severity in connective tissue diseased children, directing to early detection and better management of interstitial lung disease in CTD children. This study included 40 CTD patients divided into with and without ILD as evaluated mainly by high-resolution computed tomography (HRCT), and spirometric pulmonary function test as well as 20 normal controls to detect the expression level of KL-6 by ELISA. KL-6 levels were compared among the different study groups. In comparison of all groups of the study, KL-6 levels were related positively with both presence and severity of ILD at a cut-off of 63.4 U/ml, with sensitivity of 95.2%, specificity of 89.7%, positive predictive value of 83.26% and negative predictive value of 97.2% for ILD in CTD patients. Moreover, there is a significant inverse correlation found between serum KL-6 levels and parameter of spirometry. In conclusion, Serum KL-6 offers high sensitivity and specificity for the diagnosis of ILD in CTD children and is inversely correlated with pulmonary function deterioration. Accordingly, serum KL-6 may represent a promising biomarker for prediction and monitoring of ILD severity.

Introduction

There are more than 100 dissimilar autoimmune and inflammatory circumstances in children distressing the muscles, cartilage, joints, bones, and skin [1,2]. 294,000 children in the US have been diagnosed with a rheumatologic condition as assessed by Centers for Disease Control (CDC) which regularly first appears between the ages of 5 and 10 years, and girls are affected twofold as often as boys [3], yet prevalence in developing country not correctly estimated. Any organ system can be ed by CTD with a broad variety of disease features and severity, such as rash, arthritis, and more advanced presentation as renal or respiratory failure. The identification of CTD is frequently delayed and identifying the exact nature of CTD can be challenging[4] . In SLE, about half of patients have some form of pulmonary immersion throughout the progression of the disease [5-8].

Interstitial lung diseases (ILD) are a cluster of disorders characterized by interstitial inflammation and fibrosis, The prevelance of chILD was approximated annually; 1.3 to 3.6 per 1,000,000 in children under 17 years, 108–162 per 1,000,000 in children under 15 years[9-11]. The large disparity noted can be clarified by the difference in the population involved in each study and a difference in the criteria of ILD diagnosis. CTD related ILD (CTD-ILD) occurs with development of original disease with difference prevelance[12]. ILD is the typical presentation of respiratory system involvement in autoimmune connective tissue disease, it's not limited to the interstitium but also alveoli, pleura, vascular, lymphatic structures, and airways of all diameters may all be included in the disease. ILD when present, is frequently accompanying by significant morbidity and mortality [6].Similarly, [8,13] mentioned that Interstitial lung disease (ILD) is one of the crucial issues that impact the prognosis of connective tissue diseased patients, and can cause uninhibited systemic disease activity in CTD, it can be fatal, and early detecting of the disease is, subsequently, important. Pulmonary function tests are key in assessing CTD patients, PFT inform disease severity at first diagnosis and response

to therapy over follow up[14] . High-resolution computed tomography (HRCT) is gold corner to diagnose ILD[12,15]. The pathogenesis of ILD in rheumatic disease is complicated, multifactorial, and incompletely known[16-18]. The clinical manifestation and progression of ILD involves both inflammatory/immune and fibrotic/tissue components, which often represent a progressive uncontrolled tissue repair reaction in response to injury, finally leading to irreversible remodelling of the lung and diminished lung function [19].

Yet, it is not clear which marker (markers) can conveniently be used to determine the severity of ILD in CTD[20]. Krebs von den Lungen-6 (KL-6) is a high molecular weight, mucin like glycoprotein grouped as human MUC1 mucin produced by type II alveolar pneumocytes and bronchial epithelial cells, cellular damage and regeneration are the main stimulants[21]. It is an significant serum marker for interstitial lung disease (ILD); it can expect development of ILD in connective tissue diseased patient [22].Furthermore, Sato, Hoshino, Satoh, Fujita, Kawakami, Kuwana, Fujita [23] reported that KL-6 is positively associated with the severity of ILD, and those patients had a worse prognosis with these biomarkers.

Due to high fatality of ILD in association with CTD, the need for biochemical marker for early detection is emergency, So, our study aimed to evaluate the correlation between serum KL-6 levels with both presence of interstitial lung disease (ILD) and its severity in connective tissue diseased children, directing to early detection and better management of interstitial lung disease in CTD children.

Methods

Study population

Participants of our case control study were collected randomly from the electronic medical record database between October 2019 and April 2020 from Rheumatology and Rehabilitation Department, and Pediatric Department; Pulmonology, Immunology and Allergy Unit, children hospital. All experimental procedures were approved and formed in accordance with the guidelines of Institutional Review Board (IRB) of Faculty of Medicine, Zagazig University, Egypt (Approval No.: ZU-IRB #544459/14-7-2019).

Totally, the study include the connective tissue diseased children aged 5-15 years at primary diagnosis, according to the following classification criteria: the 2010 European League Against Rheumatism (EULAR) criteria for rheumatoid arthritis (RA)[24] , the 2019 European League against Rheumatism (EULAR) criteria for systemic lupus erythematosus (SLE)[25] , the 2017 European League against Rheumatism (EULAR) criteria for dermatomyositis (DM)[26], The 2007 Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis (SSc) [27], and The 2019 Diagnostic criteria for mixed connective tissue disease (MCTD): From the Japan research committee of the ministry of health, labor, and welfare for systemic autoimmune diseases[28]. While we exclude patients with Active malignancy, and active acute infections.

The patients were examined for presence of ILD according to according to American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease and European protocols for the diagnosis and initial treatment of interstitial lung disease in children [29-32] . The participants were divided into four groups, Group 1 (control group) consisted of (20) healthy control volunteer children; Group 2 (CTD group): included (20) connective tissue diseased children without interstitial lung disease; *Group 3 (CTD+ILD group):* which consisted of (20) connective tissue diseased children with interstitial lung disease, 16 of the were already diagnosed and 4 patients were newly diagnosed at time of study. Group 3 were subdivided according to severity of interstitial lung disease (according to the pulmonary function tests) [20] as follow: Group 3a (mildILD subgroup): which consisted of connective tissue diseased children with mild interstitial lung disease. Group 3b (severeILD subgroup): which consisted of connective tissue diseased children with severe interstitial lung disease.

Detection, Severity, and follow up of chILD

Pulmonary function test (PFT): Patients underwent the PFT using spirometry. The following parame-

ters were recorded: forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC ratio. These parameters were all expressed as a percentage of measured value/predicted value. Interpretation of PFT according to Jiang, Tao, Zuo, Li, Wang, Fang, Xu, Li [20], pulmonary function value FVC, FEV1>80% of predicted values was considered as normal, Patients were considered as having mild ILD if they had (60%<FVC, FEV1<80% of predicted values) in PFT, and Patients were considered as having severe ILD if they had (FVC, FEV1<60% of predicted values) in PFT.

Laboratory analysis

Blood samples (10 mL) were gathered from all the patients and controls, and stored at - 80 °C after centrifugation at 1000 rpm for 15 min. KL-6 levels were calculated using ELISA (Bioneovan Co., Ltd., Beijing, China) with Assay range 3.4 U/ml -200 U/ml.

Statistical analysis

Mean, standard deviation, ranges, median, range, frequency, and ratio data were calculated as descriptive statistics. The Kruskal–Wallis and Mann–Whitney U tests were used for the analysis of numerical independent data. Receiver operating characteristic (ROC) curves were set up to identify the cut off value for KL6 to differentiate patients with and without ILD, matching with the Youden method[33,34], which detect sensitivity and specificity. Estimation of the area under the ROC curve and its 95% confidence interval, Sensitivity, specificity, positive and negative predictive values related with the cut off value were all calculated. All statistical analyses were applied using SPSS for Windows 15 statistical software. A value of $p<0.05$ was statistically significant, a value of $p<0.001$ was highly statistically significant, and a value of $p>0.05$ was non-statistically significant.

Results

Demographic and clinical characteristics of patient (table 1):

The study population consisted of 40 patients with CTD, 20 of whom had ILD (12 mild, 8 severe); their data were compared to those of 20 healthy control subjects. the mean age of the study groups, in control group the mean age was 12 ± 2.4 years, versus 13 ± 2.2, 11.9 ± 3.5 years in CTD only group, CTD+ILD group, respectively, The CTD duration was 3.2 ± 2.5, 2.6 ± 1.2 CTD only group and CTD+ILD group, respectively. The ILD duration was 1 y. (min 0.; max 3 y.). With female predominance in all groups.

KL-6 estimation among different groups:

The median serum level of KL-6 was 52.3 U/mL (min 32.8; max 62.4 U/mL) in control group, 56.7 U/mL (min 35.8; max 68.5 U/mL) in CTD only group, 72.2 U/mL (min 58.4; max 100.5 U/mL) in mildILD, and 102.7 U/mL (min 76.1; max 180.8 U/mL) in severeILD group. The KL-6 levels were higher in the severeILD, then mildILD group, and lowest in control groups (table 2).

Comparison of PFT among different groups (table 3):

Spirometry represents a useful investigation for both the severity and follow up of ILD. Generally, in ILD, pulmonary function abnormalities showed a restrictive pattern with decreased lung compliance as well as lung volumes. CTD only group showed a forced expiratory volume in 1 s (FEV1) (% predicted) 101 ± 7, forced vital capacity (FVC) (% predicted) 95 ± 7, the mildILD group showed a FEV1% 77 ± 10, FVC% 72 ± 7, and the severeILD group showed a FEV1% 55 ± 5, FVC% 49 ± 8.

Associations between KL-6 serum level and spirometry results:

(figure 1) shows a significant inverse correlation between serum levels of KL-6 and predicted FEV1 (%Pred) (r = - 0.7056, P = 0.000), and also a significant inverse correlation between serum levels of KL-6 and FVC (%Pred) (r = - 0.7745, P = 0.000).

Prediction of ILD by Multivariate regression analysis and ROC curve analysis:

The most sensitive variable to detect ILD in CTD child was KL-6 and FVC%. According to the Receiver Operating Characteristic Curve (ROC) analysis, the area under the curve was of 0.977 and the cut-off value of serum KL-6 to distinguish ILD was 63.4 U/ml, with sensitivity of 95.2 %, specificity of 89.7%, positive predictive value of 83.26% and negative predictive value of 97.2% (figure 2). Moreover, FVC% Receiver Operating Characteristic Curve (ROC) analysis shows that the area under the curve was of 0.979 and the cut-off value of serum FVC% to distinguish ILD was 79, with sensitivity of 95.2%, specificity of 100%, positive predictive value of 100% and negative predictive value of 95.4% (figure 3). Comparison between KL6 and FVC% Roc curves shows that there is no statistical difference (P = 0.7385) between KL6 and FVC% ROC curves.

Discussion

Juvenile CTD is accompanied by high morbidity and mortality and can disturb any organs. Yet, ILD is an uncommon but it is one of the most significant complication of CTD [6,35]. The serum KL-6 level is secreted by type II alveolar epithelium and elevated with lung tissue regeneration [36-38]. KL-6, which is a sensitive and specific marker for the development of ILD[34,39-41]. As a result of this solid review, our study aims to evaluate the correlation between serum KL-6 levels with both presence of interstitial lung disease (ILD) and its severity in connective tissue diseased children, directing to early detection and better management of interstitial lung disease in CTD children.

Regarding to KL-6 serum level and its relationship with severity of ILD and other measured parameters, our study concluded that the KL-6 levels were increased in the CTD with ILD patients compared to the CTD without ILD and control groups. At the cut-off value of serum KL-6 to distinguish ILD was 63.4 U/ml, with sensitivity of 95.2%, specificity of 89.7%, positive predictive value of 83.26% and negative predictive value of 97.2%. Similar results were reported by Oguz et al. who detected increased KL-6 levels in CTD with ILD patients than patients without ILD and control groups [6] . In the same way, Fathi et al. reported that the KL-6 levels were increase in 12 patients with polymyositis and DM + ILD [42] . Furthermore, Fukaya et al. presented that the KL-6 level is a marker of ILD in CTD, and also indicate disease activation and follow up[43]. In that study, no correlation was found between disease duration and KL-6 level, which disagree with our study, as we concluded that there is a significant direct correlation between disease period and KL-6 level.

Regarding to associations between serum levels of KL-6 and spirometry (PFT) parameters, our study showed that there is a significant inverse correlation between KL-6 serum level and pulmonary function parameters (predicted FEV1 and FVC%) Matching to our study, the PFT is used to detect respiratory complication in CTD studies carried out by[44-46]. Although it is a non-invasive test that can be repeated easily, it requires collaboration from the patient and is difficult to do in younger children. In a study of polymyositis and DM patients, an inverse correlation was found between KL-6 serum level and PFT parameters in patients with ILD [42].moreover, Hu et al. stated that polymyositis and DM patients with ILD had a greater KL-6 levels than patients without ILD, and they also found that the KL-6 levels were significantly inversely correlated with FEV1 and FVC% [38]. Furthermore, Cao et al. proved that the elevated serum KL-6 correlates with the worsening of lung function of SSC–ILD patients [47].

It is challenging to identify strong correlation between ILD and different CTD types because of the small number of ILD patients. Also, the study sample was diverse, and we did not assess the active CTD exacerbation. Furthermore, we did not do HRCT to asymptomatic patients to reduce radiation exposure and thus asymptomatic ILD patients might be skipped. This lowers the power of our work.

Acknowledgements:

I wish to express my deepest gratefulness to all nurse staff in Pulmonology, Immunology and Allergy Unit, children hospital, Zagazig university and to all patients and their family for patience, moral support to complete this work.

Conflict of interest

The authors declare no potential conflicts of interest.

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