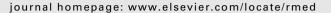


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Serial chitotriosidase measurements in sarcoidosis — Two to five year follow-up study



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KEYWORDS

Sarcoidosis; Chitotriosidase; Follow-up

Summary

Introduction: Chitotriosidase (CTO) is a human chitinolytic enzyme secreted by activated macrophages and polymorphonuclear neutrophils. Albeit not specific for sarcoidosis, it is increased in over 90% of patients with active disease. The aims of this study were to correlate CTO measurements with clinical assessment of sarcoidosis and to test CTO as a marker of sarcoidosis relapse.

Methods: 95 patients were followed-up for 24–60 months. Serial CTO measurements were performed every 3–6 months and correlated to clinical symptoms, lung function (FVC and DLco) and chest X-ray. In 38 patients clinical outcome status (COS) at 5 years was determined. Results: Initial CTO levels were significantly higher in patients with impaired FVC/DLco (p=0.011 for both) but there was no correlation with standard chest X-ray stages. Patients with Loefgren's syndrome had significantly lower initial and control CTO level compared to other patients (p=0.011 and p=0.001, respectively). At follow-up there was a positive correlation of CTO and deterioration of clinical symptoms (p<0.001), chest X-ray (p<0.001) and FVC/DLco (p=0.012 and p=0.086, respectively). Control CTO levels were significantly lower in no disease groups versus minimal or persistent disease group as defined by COS (p=0.003 and p<0.001, respectively). At relapse CTO increased for 100% or more from baseline value in 12/14 patients.

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Conclusions: It was shown that CTO correlates with certain sarcoidosis phenotypes (Loefgren's syndrome, COS) and that serial measurements of CTO correlate with clinical symptoms, chest radiographs and lung function.

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Introduction

Chitotriosidase (CTO) is a human chitinolytic enzyme secreted by activated macrophages and polymorphonuclear neutrophils. Although the role of CTO in human is still not completely elucidated, it is most likely a part of the innate immune system against chitin containing pathogens, such as fungi and some parasites [1,2]. Its expression is upregulated by INF- γ , TNF- α , LPS and GM-CSF and downregulated by IL-10 [3,4]. In population there is a common polymorphism in the CTO gene (CHIT1) — a 24-base pair duplication which results in the production in an inactive enzyme. The approximate frequency of normal subjects (wt/wt) is 60%, heterozygotes (wt/H) 34% and homozygotes (H/H) 6% [2,5,6]. Heterozygotes were reported to have about 50% of CTO activity compared to wild type, whereas homozygotes have no CTO activity in any body tissue [2].

While increased CTO is not specific for sarcoidosis [2], it was shown to be very sensitive biomarker of active sarcoidosis [7-11]. Sensitivity is estimated to about 90% which exceeds the sensitivity of commonly used biomarker angiotensin convertase enzyme (ACE) of about 60% [12]. CTO in serum and bronchioalveolar lavage (BAL) correlated with radiological stages of sarcoidosis [7,9,10]. CTO in BAL was shown to correlate with quantitative HRCT score of lung volume affected by sarcoidosis [13]. There is some evidence that CTO could have prognostic value in sarcoidosis [10]. CTO was proposed as a follow-up marker both for detecting relapses of the disease and for determining the adequate patient management [10]. It was previously shown that treatment with corticosteroids reduces the activity of CTO [8,9]. Similarly to ACE, CTO most likely reflects granulomatous burden of the disease [9,14,15] and this reduces after corticosteroid treatment is initiated in majority of patients [16,17]. On the other hand, corticosteroid resistant sarcoidosis has been described. It is characterized by increased TNF-α release of alveolar macrophages [18]. TNF- α antibodies can be efficient in such cases [19-21]. There is currently no data on how CTO changes with various treatments in corticosteroid resistant sarcoidosis.

The aims of this study were to correlate CTO measurements with clinical assessment of sarcoidosis and to test CTO as a marker of sarcoidosis relapse.

Methods and subjects

Subjects

The study comprised 100 consecutive patients with newly diagnosed sarcoidosis according to ATS/ERS/WASOG criteria [22] at the Department of pulmonary diseases of University medical centre Ljubljana, Slovenia. Patients were

prospectively included from June 2006 to May 2011 immediately after first diagnostic work-up before introduction of any treatment. In five subjects there was no CTO activity in any sample and they were excluded from further analysis (presumed to be homozygotes for CHIT1 duplication polymorphism). The data from 95 patients is reported in the results.

All subjects gave a written consent to participate in the study which was approved by the National Ethics Committee of the Republic of Slovenia (numbers 198/05/04 and 203/02/11). The patients included were corticosteroid naïve at the time of the first sampling.

Follow-up

Study subjects had regular follow-up at our clinic every 3–6 months or more often if necessary due to symptoms. There were followed-up from 24 to 60 months (median 38.5 months). Regular examinations included: clinical assessment, chest X-ray, lung function testing and CTO sampling. CTO measurements were not available to the clinician at the time of clinical examination to avoid biasing.

Blood sampling and measurement of CTO activity

Venous blood was drawn on each occasion into a tube without anticoagulant, centrifugated and immediately stored at $-20~^\circ\text{C}$. The CTO activity was determined in serum using the 22 μM 4-methylumbelliferyl- $\beta\text{-D-N,N',N''}$ -triacetylchitotriosiose (4 MU-chitotrioside, Sigma Chemical Co.) in citrate phosphate buffer (pH 5.2) as an enzymatical substrate. Five microlitres of serum or BAL was incubated with 100 μL of substrate for 1 h at 37 $^\circ\text{C}$. The reaction was stopped by adding 2.5 mL of 0.3 M glycine/NaOH buffer (pH 10.6). The reaction product, fluorescent 4-methylumbelliferone, was measured using a Perkin–Elmer fluorimeter at excitation wave length 365 nm and emission 465 nm. The CTO activity was expressed in nmol/h/mL.

Clinical symptoms assessment

At presentation symptoms such as fever, fatigue, joint pain, cough, dyspnea or chest pain were documented. At follow-up visits the symptoms were graded as new, persisting or none. The patients presenting with acute clinical picture consisting of bihilar lymphadenopathy, erythema nodosum and arthalgia were considered to have Loefgren's syndrome. Screening for extrapulmonary sarcoidosis was done in all patients. The patients were not systematically evaluated for pulmonary hypertension. In cases of persistent dyspnea and persistent low diffusion for carbon monoxide echocardiography was done but there were no cases of pulmonary hypertension.

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