Clinical Immunology (2009) **131**, 216–222

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/yclim

Plasma chitotriosidase activity in multiple sclerosis

M. Comabella [a,*], C. Domínguez [b,c], J. Rio [a], P. Martín-Gallán [b,c], A. Vilches [b,c], N. Vilarrasa [a], C. Espejo [a], X. Montalban [a]

[a] *Centre d'Esclerosi Múltiple de Catalunya, CEM-Cat, Unitat de Neuroimmunologia Clínica, Hospital Universitari Vall d´Hebron (HUVH), Barcelona, Spain*
[b] *Molecular Biology and Biochemistry Research Center (CIBBIM), Hospital Universitari Vall d´Hebron (HUVH), Barcelona, Spain*
[c] *Center for Biomedical Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Barcelona, Spain*

Received 8 October 2008; accepted with revision 9 December 2008
Available online 26 January 2009

KEYWORDS
Multiple sclerosis;
Interferon-beta;
Chitotriosidase;
Innate immunity

Abstract A recent study has shown that chitotriosidase (Chit) may play a role in the pathogenesis of multiple sclerosis (MS). Plasma Chit activity was investigated in 219 untreated MS patients and 160 healthy controls (HC) by means of a fluorometric enzyme activity assay. Chit activity was also measured in a subgroup of 46 patients following treatment with interferon-beta (IFNβ). Overall, plasma Chit activity was significantly increased in MS patients compared with HC, but no differences were observed between relapsing and progressive clinical forms. In addition, Chit activity was similar between patients during relapse and patients during clinical remission. Treatment with IFNβ was associated with a significant increase in Chit activity compared with untreated patients in both responders and non-responders to treatment. Although these findings suggest a role of Chit in MS, our data do not support an association between plasma Chit activity and MS clinical course and clinical response to IFNβ treatment.

Introduction

Human chitotriosidase (Chit) is a member of the chitinase family, a group of glycoside hydrolases that cleaves chitin. Chitin is a polysaccharide present as a structural component in fungi, nematodes, insects and shellfish, but not in humans. Chit is present in normal plasma [1] and is mainly secreted by activated macrophages and, to a lesser degree, by neutrophils [2,3]. Chit activity is markedly increased in patients with lysosomal storage diseases [4], especially in Gaucher disease [5]. Chit activity is also found elevated, although to a lesser extent, in thalassemias [6], arteriosclerosis [7], parasitic infections such as malaria [8], and sarcoidosis [9].

Little is known about the physiological function of Chit, although its phagocyte-specific expression points to a role of the enzyme in innate immunity providing protection against chitin-containing pathogens. A common polymorphism in the Chit gene exists in which a 24 bp duplication in exon 10 results in the activation of a cryptic 3′ splice site and deletion of 87 nucleotides [10]. The resulting phenotype is an asymptomatic Chit activity deficiency. Interestingly, an enzymatically inactive protein is observed in around 6% of Caucasians [11] but is very rare in Africa where parasitic disease is endemic [12].

Chit activity in multiple sclerosis (MS) has received little attention. A recently published paper by Sotgiu et al [13]

* Corresponding author. Unitat de Neuroimmunologia Clínica, CEM-Cat. Edif. EUI 2ª planta, Hospital Universitari Vall d'Hebron. Pg. Vall d'Hebron 119-129 08035 Barcelona, Spain. Fax: +34932746084.
E-mail address: mcomabel@ir.vhebron.net (M. Comabella).

1521-6616/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.clim.2008.12.004

showed a significant increase in plasma and cerebrospinal fluid (CSF) Chit levels in MS patients compared with healthy controls and patients with other neurological diseases. Interestingly, plasma Chit activity was significantly higher in patients with progressive forms of MS, and in patients with moderate to severe neurological disability as measured by the Expanded Disability Status Scale (EDSS). The authors proposed Chit activity as a novel marker of MS clinical deterioration.

Based on these findings, the purpose of the present study was to widen our knowledge on the role of Chit in MS pathogenesis by determining plasma Chit activity in a large cohort of MS patients that included patients during relapses and those treated with interferon-beta (IFNβ).

Methods

Patients

One hundred sixty healthy controls and 219 patients with clinically definite MS who had not received treatment with corticosteroids in the 3 months before blood sampling were included in the study. The study was approved by the Ethics Committee of Vall d´ Hebron University Hospital and all the subjects involved in the study gave their written informed consent.

Chit activity and MS clinical course

To investigate plasma Chit activity in patients with different clinical phases of MS, the disease course of individual patients was labelled as relapsing-remitting (RRMS, $n=87$), secondary progressive (SPMS, $n=39$), or primary progressive (PPMS, $n=58$) according to the Lublin and Reingold classification [14]. None of these patients had ever received treatment with interferon-beta (IFNβ) or other immunosuppressive therapy.

Chit activity and relapses of RRMS

To ascertain whether plasma Chit activity is altered during clinical exacerbations, plasma Chit activity was determined both in patients whose blood was drawn during clinical remission ($n=87$) and at the time of an acute relapse ($n=35$), defined by the appearance of new neurological symptoms or worsening of pre-existing neurological symptoms attributable to MS which persisted for over 24 hours.

Demographic and baseline clinical characteristics of MS patients and healthy controls are summarized in Table 1.

Chit activity during treatment with IFNβ

In order to study the effect of IFNβ on Chit activity, enzyme activity was measured in a subgroup of 46 patients from the RRMS group after receiving treatment with IFNβ for a median time of 8 months (range: 5–10 months). Twenty-three patients were treated with subcutaneous IFNβ-1b, 16 patients with intramuscular IFNβ-1a, and 7 patients with subcutaneous IFNβ-1a. As shown in Table 1, the subgroup of IFNβ-treated patients was representative of the group of RRMS patients in clinical remission.

Chit activity and clinical response to IFNβ treatment

To assess the role of Chit in the clinical response to IFNβ, treated patients were further classified into responders and non-responders to therapy. Clinical criteria of response to IFNβ were applied after two years of treatment. Patients were labeled as responders when there was no increase in the EDSS score and no relapses during the follow-up period. Patients were classified as non-responders when one or more relapses occurred during the follow-up period and when an increase of at least 1 point was observed in the EDSS score that persisted for a minimum of two consecutive scheduled visits separated by a 6-month interval [15]. Patients with intermediate response phenotypes, i.e., presence of relapses and increase of less than 1 point in the EDSS score or absence of relapses with increase in the EDSS were not included in the study.

Chit activity and clinical and radiological variables

Plasma Chit activity was correlated with clinical variables such as disease duration, number of relapses in the previous two years, and EDSS at the time of blood sampling. In the group of patients with PPMS, Chit activity was also correlated with radiological variables such as T2-weighted lesion load

Table 1 Demographic and baseline clinical characteristics of MS patients and HC

	RRMS			SPMS	PPMS	HC
Characteristics	in remission	in relapse	IFN-treated			
N	87	35	46	39	58	160
Female/male (% women)	58/29 (66.7)	23/12 (65.7)	30/16 (65.2)	25/14 (64.1)	29/29 (50.0)	96/64 (60.0%)
Age (years) [a]	34.9 (7.0)	31.6 (9.5)	34.0 (8.3)	45.7 (8.5)	47.4 (8.8)	40.4 (7.3)
Duration of disease (years) [a]	6.5 (5.9)	5.7 (5.8)	7.5 (6.7)	12.4 (7.2)	10.9 (6.7)	–
EDSS [b]	2.4 (1.5–3.0)	3.0 (2.5–3.5)	2.3 (1.5–3.5)	4.8 (4.0–5.8)	6.0 (4.0–6.0)	–
Number of relapses in the 2 previous years [a]	2.5 (1.2)	1.7 (1.8)	2.9 (1.2)	0.9 (0.9)	–	–

EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; IFN: interferon; HC: healthy controls.

[a] Data are expressed as mean (SD).

[b] Data are expressed as median (interquartile range).