Automated system to detect low-grade underlying inflammatory profile: Gaucher disease as a model

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Abstract

Patients with Gaucher disease, perhaps due to chronic storage of glycolipids, apparently harbor a subclinical or underlying inflammation. Quantification of a baseline inflammatory profile in patients with Gaucher disease is more impressive when compared with that of matched healthy controls in a systematic, automated fashion. A mean of 16 healthy controls was generated for each of 50 patients with Gaucher disease by applying variables relating to potential for inflammatory features, for example, atherothrombotic risk factors. Relative to matched controls, male patients with Gaucher disease had significant elevations in fibrinogen (312 ± 61 vs. 244 ± 21 mg/dl; \( P = 0.002 \)), accelerated erythrocyte sedimentation rate (ESR) (21.5 ± 16.1 vs. 7.0 ± 1.4 mm/H; \( P = 0.004 \)), and elevated high-sensitivity C-reactive protein (hs-CRP) (1.4 ± 2.4 vs. 0.9 ± 1.6 mg/l; \( P = 0.026 \)). Comparison of female patients versus controls revealed significant elevations in fibrinogen (337 ± 81 vs. 273 ± 19 mg/dl; \( P < 0.0005 \)) and accelerated erythrocyte sedimentation rate (33.1 ± 22.2 vs. 15.6 ± 3.1 mm/H; \( P < 0.0005 \)). Enzyme replacement therapy for Gaucher disease did not affect these values. Comparison with the matched healthy controls highlights the true low-grade inflammatory profile in Gaucher disease. By employing information from well-matched controls, even low-grade inflammatory conditions that may have otherwise been considered “within normal limits” can be teased out. This approach is not disease-specific and can be easily applied to any acute or subacute inflammatory disease/condition.

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Introduction

Recent studies suggest that apparently healthy individuals harbor an underlying, low-grade, subclinical inflammation \([1–4]\). A corollary of this finding is that individuals who come to medical attention with an acute or subacute inflammatory disease actually present with the current complaint superimposed on an underlying inflammation that is unique to age, sex, and sociomedical background.

Gaucher disease, the most common storage disorder, is caused by mutations in the gene encoding the lysosomal enzyme, \( \beta \)-glucocerebrosidase, leading to the accumulation of glucocerebroside in the cells of the monocyte–macrophage system \([5]\). It has been posited that chronic storage stimulates a disease-specific low-grade inflammation \([6–11]\). Therefore, acute inflammatory processes in Gaucher disease, whether overt or subclinical, would be secondary to chronic stimulation by the storage cells and may have

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prognostic and therapeutic implications, similar to those currently appreciated in atherosclerosis [1].

A multivariable database from healthy controls with characteristics such as age, sex, anthropometric measurements, atherothrombotic risk factors, and smoking habits, as well as concomitant inflammation markers such as fibrinogen and erythrocyte sedimentation rate, was established to provide inflammatory profiles that can be retrieved automatically and used to highlight abnormal inflammatory responses in patients with chronic diseases.

The purpose of the current study was to ascertain the extent of the putative inflammatory baseline in patients with Gaucher disease relative to matched healthy controls.

Materials and methods

Patients with Gaucher disease

An unselected cohort of adult patients with Gaucher disease was taken from those routinely followed in the Gaucher Clinic at the Shaare Zedek Medical Center (Jerusalem, Israel), whether receiving enzyme replacement therapy (Cerezyme®, Genzyme Corporation, MA, USA), oral substrate reduction therapy (Zavesca®, Actelion Pharmaceuticals Ltd.), or untreated.

Control population

The database of the Tel Aviv Medical Center Inflammation Survey (TAMCIS) [12] was used for matching controls. The TAMCIS is a cross-sectional survey of apparently healthy employees and former employees of the Tel Aviv Sourasky Medical Center and Tel Aviv Municipality (Israel), and of individuals evaluated at the Medical Center outpatient screening programs, as well as patients in routine follow-up at outpatient clinics for diabetes, hypertension, metabolic disorders, or with atherothrombotic risk factors. All individuals included in the present survey gave written informed consent according to the instructions of the Institutional Ethics Committee. Recruitment was via advertisements in employee pay stubs or personal appeals to patients in outpatient clinics.

Excluded patients and controls

Excluded were individuals in either group with evidence of cardiovascular diseases (e.g., myocardial infarction, coronary artery bypass graft surgery, peripheral artery occlusive disease, or cerebrovascular accident), cardiovascular risk factors (e.g., diabetes mellitus, hypertension, or hypercholesterolemia), or a history of smoking. Excluded also were individuals treated with steroids or nonsteroidal anti-inflammatory medication other than low-dose aspirin (<325 mg/day).

Inflammatory biomarkers

The erythrocyte sedimentation rate (ESR) was determined by the method of Westergen [13], fibrinogen by the method of Clauss [14] using a Sysmex 6000 (Sysmex Corporation, Hyaga, Japan) analyzer, and high-sensitivity C-reactive protein (hs-CRP) concentrations using a Boering BN II Nephelometer (DADE Boering, Marburg, Germany) [15].

Statistical methods

Controls were matched to each patient by age (approximately ±2 to 3 years) and by body mass index (BMI) (approximately ±1.5–2.5 kg/m²). Values were averaged for the controls of each patient. The averaged control values were compared to the patient values using the Wilcoxon rank sign test, a nonparametric test for paired samples. Data were summarized and displayed as mean ± standard deviation.

High-sensitivity CRP has a nonnormal distribution, so logarithmic transformations were employed with results expressed as high-sensitive CRP back-transformed to geometric mean ± standard deviation.

Results

For each of 50 patients, there were 4–31 (mean = 16.1; total = 803) controls. There were no significant differences in age or BMI between patients and controls (Table 1).

The results of inflammatory biomarkers are presented in Table 2. Erythrocyte sedimentation rate and fibrinogen were significantly elevated in both male and female patients, while high-sensitivity CRP was elevated only in the male patients. Treatment status is shown in Tables 3 and 4 for male and female patients, respectively. Erythrocyte sedimentation rate and fibrinogen were significantly elevated in both male and female patients regardless of specific treatment for Gaucher disease.

Discussion

The concept of a database of sociomedical characteristics and laboratory tests derived from apparently healthy individuals to highlight acute and/or chronic inflammation is new. There are multiple factors that might affect the intensity of an individual’s underlying inflammatory profile including age [5], sex [16], BMI [17], some medications [18], components of the metabolic syndrome [19], smoking [20], physical activity [21], the intake of alcohol [22], recent infection/inflammation, etc. Thus, at any given point, a patient with comparable sociomedical values can be matched with the database of controls in order to highlight the specific contribution of a specific disease process.
At present, only four inflammatory biomarkers are available at the Inflammation Data Center, including white blood cell count and differential, erythrocyte sedimentation rate, quantitative fibrinogen, and high-sensitivity CRP. These were chosen as representatives of the acute phase response, with considerations of cost-effectiveness calculations as well as these being among the most commonly requested inflammatory biomarkers in daily practice. In addition, these are well standardized and are performed routinely in most clinical laboratories requiring no unusual instrumentation and/or reagents. The concomitant use of four biomarkers covers the entire time course of the acute phase response [23].

In patients with Gaucher disease, the existence of a low-level chronic inflammatory profile has been posited but has not been used for prognostic purposes. Indeed, in many instances, results of inflammatory markers from patients with Gaucher disease could be consistently seen as within the “normal” range. On the one hand, this speaks to the issue of what is a true “normal” value, for example, prior to introduction of high-sensitivity CRP, values <5 mg/l were considered within normal limits, whereas today, values >3 mg/l are considered to have an enhanced atherothrombotic risk [3]. Similarly, there are prognostic considerations for the overlying inflammatory profile and thereby enhance the specific implications of an elevated value.

Finally, but of considerable interest, is the fact that specific treatment for Gaucher disease, particularly the use of exogenous enzyme, did not affect any of these markers. This finding may imply that the underlying inflammatory condition in Gaucher disease is not secondary to stored lipids per se: if this is the case, exogenous enzyme by virtue of decreasing stored material should induce improvement. Alternatively, we may postulate that the subclinical inflammatory status in Gaucher disease is a tertiary response (i.e.,...
in response to a cytokine or chemokine elaborated secondary to glycolipid storage) or that the inflammatory condition is not at all specific.

In conclusion, by employing information from well-matched controls, even low-grade inflammatory conditions that may have otherwise been considered “within normal limits” can be teased out. This approach is not diseasespecific and can be easily applied to any acute or subacute inflammatory disease/condition.

References