Fibromyalgia and Gaucher’s disease

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Summary

Background: Patients with symptomatic Gaucher’s disease sometimes have non-specific symptoms (such as general malaise with widespread musculoskeletal pains) that respond poorly to enzyme replacement treatment. These may indicate fibromyalgia syndrome; if so, other therapeutic options might be more appropriate.

Aim: To identify patients with Gaucher’s disease for whom fibromyalgia-specific therapy may be therapeutic.

Design: Questionnaire-based survey.

Methods: Adult patients (n=109) with non-neuronopathic Gaucher’s disease and adult healthy controls (n=108) completed health-related questionnaires including the Fibromyalgia Impact Questionnaire, and underwent testing with a dolorimeter to ascertain sensitivity at 22 tender points.

Results: Six patients, but no controls, met the criteria for fibromyalgia. Patients with fibromyalgia had a significantly greater incidence of co-morbidities (p=0.014) relative to other patients with Gaucher’s disease; four suffered from bone involvement and were receiving enzyme therapy, but two were untreated.

Discussion: The presence of fibromyalgia-specific trigger points may result from multiple aetiologies, or may be an independently-sorting predisposition. Our findings cannot distinguish between these possibilities, but if fibromyalgia were the cause, enzyme replacement therapy would be expensive and inappropriate.

Introduction

Gaucher’s disease, the most common lysosomal storage disease, is inherited as an autosomal recessive disorder and is caused by deficiency in the β-glucocerebrosidase gene. The resulting accumulation of glucocerebroside is primarily stored in the cells of the monocyte-macrophage system, causing various and variable signs and symptoms in this multi-system disorder.1 There are neuronopathic forms of the disease (types II and III), but type I (the non-neuronopathic form) is the most common, and although pan-ethnic, is more common in Ashkenazi Jews.2 Clinical manifestations may be severe: splenomegaly, hypersplenism and even splenic infarction; liver involvement causing hepatomegaly; involvement of the bone marrow; as well as bone involvement such as osteopenia, bone pain, pathological fractures, and avascular necrosis of the large joints. The majority of patients homozygous for the most common mutation, N370S (1226G), however, have mild disease or may be asymptomatic.3 Patients with symptomatic disease have been able to benefit from safe and effective treatment that induces reduction in hepatosplenomegaly and near-normalization of haematological...
features, with improvement of quality of life, but such treatment is quite expensive.

As the number of patients requiring medical intervention increases, particularly in large referral clinics, awareness of less common features of Gaucher’s disease has been increasing, and similarly there is growing appreciation that patients with Gaucher’s disease may be predisposed to other diseases that sort independently. The latter situation is highlighted when symptomatic patients do not respond to enzyme replacement with improvement in complaints and/or signs.

One of the more prominent symptoms for which patients with Gaucher’s disease require medical attention is that of general malaise, with widespread musculoskeletal aches and pains. Because of anaemia, fatigue is not uncommon; because of bone disease, aches and bone pains are often presenting signs as well as chronic conditions; and because of chronic disease and/or pain, sleeplessness with headaches and paresthesias and even depression can be expected in Gaucher’s disease, yet these are not necessarily responsive to enzyme therapy in all patients. When viewed as a composite, however, these latter symptoms and signs may be indicators of fibromyalgia syndrome, and if this is the true aetiology, other therapeutic options might be recommended.

The diagnosis of fibromyalgia syndrome may be based on a conglomerate score of five items, including trigger points and degree of musculoskeletal tenderness and pain; nonetheless it is still a rather amorphous diagnosis that essentially reflects fatigue and non-specific complaints that may be categorized differently by different physicians. However, a telling indicator of fibromyalgia is the synergistic effect of complaints ascribable to fibromyalgia when there is co-morbidity that may act as a stressor. This may explain the more than additive effect of chronic diseases with fatigue or pain components on patients who suffer from fibromyalgia. Similarly, some thyroid autoimmune pathology has been correlated with fibromyalgia, implying a biochemical predisposition in some cases. Finally, based on animal studies, fibromyalgia is seen as relentless sympathetic hyperactivity that is responsive to sympathetic blockade, implicating a form of dysautonomia.

Since there are many patients with Gaucher’s disease who have rather mild signs of Gaucher’s disease but nonetheless complain of symptoms that intuitively may be suggestive of fibromyalgia syndrome, the current study was undertaken to assess the incidence of true fibromyalgia syndrome among patients with Gaucher’s disease. The underlying purpose was to identify those patients for whom fibromyalgia-specific therapy may be therapeutic, vs. attempting to maintain these same patients on enzyme replacement therapy for lack of an alternative explanation for their symptoms.

Methods

Patients arriving for routine follow-up examinations at a large referral clinic were asked to participate in this study. A group of 108 healthy Ashkenazi Jewish individuals, with no histories of chronic disease, served as controls.

All subjects were questioned regarding age, gender, family status, income and education for the demographic characteristics, and were asked to complete the Fibromyalgia Impact Questionnaire by assessing the severity of the following symptoms/medical problems on a scale of 0 to 10, where 0 indicates complete lack of the symptom, and 10 describes the worst degree of suffering:

(i) symptoms of pain, anxiety, depression, fatigue, morning stiffness, and general well-being;
(ii) the influence of their general physical and mental condition on their well-being during the preceding week;
(iii) the existence of paraesthesia, headache, and sleep disturbance.

Depression and anxiety were evaluated by the AIMS scales and Hopkins Symptom Checklist 90 for anxiety (SCL 90-ANX) questionnaire and general quality of life by the Short Form (SF)-36 questionnaire.

Patients’ medical history was summarized from medical files, as well as calculated using a Severity Score Index (SSI) which is a score from 0 to 30 points, based on the presence of disease parameters at presentation, where <10 points = mild disease, 11–20 points = moderate disease, and >21 points = severe involvement.

The diagnosis of fibromyalgia syndrome was established according to the 1990 criteria and classification of the American College of Rheumatology. The 18 specific tender points and the four control points were assessed by both a dolorimeter and manual pressure application.

Institutional Review Board approval was given for this study.

Results

Of 109 patients with Gaucher’s disease, six patients (five females) were identified as having fibromyalgia syndrome, while none of the control group met the
criteria. Clinical characteristics of the six patients are presented in Table 1.

Age at Gaucher’s disease diagnosis, often an indicator of severity, was no different between those who did and those who did not have fibromyalgia (1–40 years and 19–46 years, respectively). However, these six patients had a higher mean SSI (15.7 ± 7.8) than the other patients (10.6 ± 5.9) with Gaucher’s disease.

Patients with fibromyalgia had a significantly greater incidence of co-morbidities (p = 0.014) than the other patients with Gaucher’s disease in the study.

Four identified patients with fibromyalgia (67%) were receiving enzyme replacement therapy, vs. 33% of the other patients with Gaucher’s disease (p = 0.018). Four patients with fibromyalgia suffered from severe bone involvement (e.g. avascular necrosis of a large joint or pathological fractures) vs. 33% in the remaining patients (p = 0.018).

Table 2 presents fibromyalgia-specific symptoms among patients with Gaucher’s disease, relative to the controls. Although there were no statistically significant differences between patients and controls with regard to the numbers of fibromyalgia-specific tender points or control points, patients with Gaucher’s disease had significantly more complaints of morning stiffness and tender points.

Table 3 presents comparison of scores and fibromyalgia-specific symptoms on the scales used...
to assess depression and anxiety. Whereas there were statistically significant greater numbers of symptoms among patients with Gaucher’s disease, there was no significant difference in depression or anxiety scales.

Discussion
Type I Gaucher’s disease, particularly in those with the N370S mutation on one allele, is a chronic disease with variable expression. The majority of patients have a mild phenotype, but a smaller percentage have moderate to severe disease that responds well to enzyme replacement therapy, particularly if initiated early. A hallmark of the latter group is some degree of skeletal involvement: in some cases ‘only’ non-specific arthralgia and bone pain, but in most adult patients who have bone involvement, chronic pain with progression over decades, and often with sequential involvement of several large joints as well as the spine. Secondarily, there is the chronic pain of unequal distribution of weight, and the consequences of limb-length discrepancies, etc.

The fact that patients with Gaucher’s disease did not score differently than healthy controls on depression and anxiety scales may have its underpinning in that many of these patients are being treated with enzyme replacement and hence believe that they are receiving maximal benefit available to individuals with Gaucher’s disease. This facet of the study is difficult to verify relative to patients with other chronic diseases. However, in a study of patients with chronic liver disease, psychiatric co-morbidity and active medical co-morbidity (and not severity of the basic disease) correlated with reduced quality of life and scales of depression and anxiety.

The pain of fibromyalgia has been successfully treated with the serotonin receptor (5-HT) antagonist tropisetron, but this may be due to its effect on the gut. Nonetheless, if fibromyalgia is not Gaucher-related, trials of similar therapeutics may be considered appropriate. One of the six patients identified in this study has irritable bowel syndrome as a co-morbidity.

It has also been hypothesized that the underlying disturbance in fibromyalgia is in tryptophan metabolism. In a study of tryptophan depletion among 17 patients with fibromyalgia vs. 17 healthy controls, patients and controls reacted similarly with respect to all markers tested, except that in patients with fibromyalgia (but not controls) interleukin (IL)-6 levels increased significantly. These data may suggest a biochemical basis in fibromyalgia such as altered tryptophan metabolism, where tryptophan depletion activates 5-HT metabolism and IL-6 production. In normal controls, an experimental and transient disruption in global monoamine function, e.g. by tryptophan depletion, does not stimulate IL-6 production. However, in Gaucher’s disease, concentrations of IL-6 are significantly elevated; moreover, one of the IL-6 (174G → C) promoter polymorphisms (C/C genotype) may be associated with a milder Gaucher’s phenotype, and may serve as a mitigating genetic modifier.

The patients with fibromyalgia in the current study are marked by having a high SSI and more commonly bone disease (Table 1), and as such, four of these patients receive enzyme therapy. In addition, each of the four has a serious concurrent chronic disease. The presence of fibromyalgia-specific trigger points may result from either of these aetiologies, or of their combination, or may be an independently-sorting predisposition. We cannot distinguish between these possibilities on the findings of this study.

However, two of the patients, one with bone involvement and both with concomitant diseases, do not receive enzyme replacement therapy. In the interim period after completion of the original study, a further patient was examined by one of the authors (DB) and found to meet the criteria for fibromyalgia. This female patient, today 35 years old, was diagnosed 14 years ago as having Gaucher’s disease because of complaints of malaise and fatigue; Gaucher’s-specific signs and symptoms were mild (SSI = 7 points), and she has suffered no deterioration since diagnosis. For this reason, she was reluctant to initiate enzyme therapy, even though her level of daily activity is lower than that of her peers, and she can only work part-time and not consistently. With a diagnosis of fibromyalgia, alternative approaches can be recommended. From the perspective of the patient, the diagnosis of fibromyalgia affords better clinical management without treating the Gaucher’s disease, which in her case is stable and does not require treatment. This may also be of importance on the societal level, because of the expense of enzyme therapy: a saving of about US$100,000 annually for each of these patients in Israel; in countries where the dosage is four times that in Israel, the savings would be correspondingly greater. This seventh patient illustrates the potential importance of the diagnosis of fibromyalgia in a patient with very mild Gaucher’s disease, who may benefit from specific symptomatic therapy rather than being given enzyme treatment.

In evaluation of mild patients in particular, but potentially all patients with Gaucher’s disease,
examination of the 11 tender points for fibromyalgia may be an appropriate addition to the standard physical examination.

References