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Incidence of malignancies among patients with type I Gaucher disease from a single referral clinic

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Abstract

Background. It has been implied that the incidence of malignant disorders is increased in patients with non-neuronopathic (type I) Gaucher disease. The purpose of the study was to ascertain numbers of cancers in type I Gaucher disease since this is of considerable concern to patients and physicians.

Methods. Records of 505 patients with type I Gaucher disease seen at a large referral clinic since 1990 were culled in December 2004 to ascertain diagnosis of a cancer identified during follow-up. Age-matched data from the Israeli National Cancer Registry (INCR) database were used for comparison.

Findings. Patients diagnosed with cancer before 1990 were not included. Of the remaining 500 patients, 227 (45.4%) were male, mean age = 38.7 years; and 273 (54.6%) were female, mean age = 37.0 years (SD = 21.0 years for both). Twenty patients (4.0%) had developed a cancer through December 31, 2003: 6 were male and 14 were female. The most common were three cases each of lymphoma and myelodysplastic syndrome and two cases of multiple myeloma. There was no statistically significant excess of cancer rate among patients relative to age-matched rates reported in national Jewish Israeli and Ashkenazi Jewish Israeli registry records.

Conclusions. There appears to be no excess risk for hematological or other cancers among patients with type I Gaucher disease relative to the overall Jewish population matched for age. This study confirms recent international studies of patients with Gaucher disease for no excess risk for all cancers but multiple myeloma where these latter studies implicate a significantly higher incidence.

Keywords: Gaucher disease; Cancer; Hematological cancers; Multiple myeloma; MGUS

Introduction

Gaucher disease, the most prevalent lysosomal storage disease, is caused by an inherited deficiency of β-glucocerebrosidase and results in progressive hepatosplenomegaly with consequent thrombocytopenia and anemia and bone involvement [1]. It has been implied that the incidence of malignant disorders is increased in patients with non-neuronopathic (type I) Gaucher disease: two decades ago, in a post-mortem series of 35 patients who had died, about half had malignant tumors [2]; and a decade later, a study found that about one-fifth of 48 patients diagnosed with type I Gaucher disease and followed in a hematology clinic had malignancies [3].

We therefore studied the incidence rate of cancers in a large referral clinic wherein the majority are Ashkenazi Jewish patients with mild type I disease, and hence many do not require enzyme replacement therapy [4]. Results from the international registry of patients with Gaucher disease, most of whom receive enzyme treatment were also available [5]. The purpose of the study was to ascertain numbers of cancers in type I Gaucher disease since this is of considerable concern to patients and physicians.

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Methods

Records of 505 patients with type I Gaucher disease seen at a large referral clinic since 1990, with monitoring at 6- or 12-month intervals, were culled in December 2004 to ascertain diagnosis of a cancer identified during follow-up. A linkage to the Israeli National Cancer Registry (INCR) database was performed. The INCR is a population-based central tumor registry that was established in 1960; reporting to the registry is mandatory since 1982 and covers all medical facilities in the country, both public and private. All demographic data, including place of birth and immigration date, as well as residential and other personal data are stored in the central population registry.

Statistical methods

Person–years for the cohort from January 1, 1990 through December 31, 1993 were calculated; person–years calculation was interrupted for those who were diagnosed with cancer at the day of diagnosis. Person–years calculations were performed separately for males and females and age-matched. Expected cancer cases for the cohort were calculated, first using the overall Israeli Jewish population as a reference and then using the Israeli Jewish population born in European and American (Ashkenazi) countries, both of which were matched for age. 95% confidence intervals for each comparison were determined as well as the Standardized Incidence Ratio (Table 2).

Results

Cancer had been diagnosed in five patients before 1990, and therefore these were not included. Of the remaining 500 patients, 227 (45.4%) were male, mean age = 38.7 years; and 273 (54.6%) were female, mean age = 37.0 years (SD = 21.0 years for both). Twenty patients (4.0%) had developed a cancer in this period through December 31, 2003: 6 were male and 14 were female (Table 1). The most common were three cases each of lymphoma and myelodysplastic syndrome and two cases of multiple myeloma. There was no statistically significant excess of cancer rate in the cohort of patients relative to age-matched INCR database records. Although there was a trend towards excess of cancers among female patients, this was not statistically significant.

Table 2 presents the results of 95% confidence intervals and the Standardized Incidence Ratio (SIR) for comparison between the cohort of patients relative to the entire Jewish Israeli population as an index of incidence in Israel and relative to the entire putatively Ashkenazi Jewish Israeli population because of the predilection of type I Gaucher disease in our referral clinic among Ashkenazi Jews; the 6 Arab patients (members of two related families) with type I Gaucher disease, none of whom have a malignancy, were not included.

Table 1
Distribution of cancer cases in the Gaucher cohort (number of observed cases)

Disease site	Female	Male
Non-Hodgkins lymphoma	3	–
Myelodysplastic syndrome	2	1
Multiple myeloma	1	1
Prostate	–	3
Colon	1	1
Melanoma of skin	2	–
Liver	1	–
Breast	1	–
Cervix uteri	1	–
Lip	1	–
Thyroid	1	–
Total	14	6

Discussion

In a post-mortem series of 35 patients, Lee noted 19 (54%) malignant tumors [2] and postulated an association of malignancy with milder forms of Gaucher disease, which implicates the cumulative pathology of stored glycolipid. Shiran et al. reported a 20.8% incidence of cancer among 48 patients with Gaucher disease compared with 6.8% in a healthy population [3], but this study was a result of a search through the archives of a medical center that did not have a Gaucher clinic at that time, and therefore, half of the patients presenting with malignancies were identified as having Gaucher disease because Gaucher cells were found in bone marrow smears. Thus, the alarming 14.7-fold risk of hematopoietic malignancies and 20.8 fold risk of all cancers may reflect ascertainment bias.

Other than the above series, 23 cases with concurrence of Gaucher disease and malignancy have been reported [6–26], with six patients suffering from bone cancer [24].

In the current series from Israel, malignancies occurred at less than the 6.8% rate of the Israeli control population in Shiran et al. [3]. The eight hematological cancers (lymphoma, myelodysplastic syndrome, and multiple myeloma) in the current cohort is also less than the 10.4% reported by Shiran et al. [3]. No cases of bone tumors were noted in this cohort. Thus, when assessing adult Ashkenazi Jewish patients with type I Gaucher disease with generally milder disease because of the common N370S (1226G) mutation, statistics do not confirm an increased rate of either hematological or other cancers in Gaucher disease. This is of relevance to concerned patients aware of the earlier study from the lay media because of assertions of causality.

Table 2
Results of 95% confidence intervals and the Standardized Incidence Ratio (SIR) for comparison between cohort of patients with Gaucher disease relative to age-matched data from the entire Jewish Israeli population and relative to the entire putatively Ashkenazi Jewish Israeli population (based on person–years calculations January 1, 1990–December 31, 1993 with person–years calculation interrupted on day of diagnosis of cancer)

Reference population	Gender	SIR	95% confidence intervals
Entire Jewish	Male	0.7	0.13–1.19
Israeli population	Female	1.6	0.8–2.4
Entire Jewish	Male	0.6	0.12–1.1
Israeli population: Ashkenazi descent	Female	1.4	0.7–2.2

Rates of cancers other than multiple myeloma are within norms predicted from current American actuary tables [27,28]. Breast cancer appeared in only one patient in this cohort, comparable to international registry data [5]. This may actually be a confounding variable because of predilection of type I Gaucher disease among Ashkenazi Jews wherein rates of breast cancer are relatively high. For three common Ashkenazi Jewish mutations in BRCA1 and 2, relative risks are estimated as 21.6–7.6 depending on age for BRCA1 and 3.3–4.6 for BRCA2 [29]. Breast cancer among all Israeli women in 1998 (more recent data unavailable) was 95/100,000; in women with Gaucher disease, the rate is comparable [28].

The preponderance of the N370S mutation among Ashkenazi Jews has apparently mitigating effects on disease expression. Thus, there was no significant difference in statistical analyses performed on the cohort of patients relative to the entire Jewish Israeli population (using patient–years and age- and sex-matching) nor relative to the entire Jewish Israeli population of Ashkenazi ethnicity (Table 2). However, mutations associated with more severe disease are more common among non-Jews. In a collaborative preliminary report of prevalence of cancers in 144 mostly non-Jewish Dutch and German patients, there were six hematological cancers (4.2%), including two cases of amyloidosis, and an overall cancer incidence of 10.4% [30]. Thus, the rate of hematological cancers was not different to that reported herein.

In a very recent publication citing the results garnered from an international registry of 2742 patients with all types of Gaucher disease, not including the contribution of the clinic presented herein, it was concluded that overall risk of cancers and risk for cancers of the breast, prostate, colorectal, lung, and hematolgic malignancies other than myeloma were not statistically significantly higher than expected in an American population of similar age and sex [5].

International incidence of multiple myeloma is reported as 3/100,000 [28]. Herein, two adult patients had multiple myeloma, comparable to international registry data [5] and Dutch–German data where 1 patient (0.7%) is reported [30]. These findings underscore anecdotal reports of putatively increased incidence of multiple myeloma in Gaucher disease [2,3,6,8,16,18,22] but surprisingly not relative to that in the INCR. Whereas it is unlikely that multiple myeloma is selectively under-reported to the INCR, one may speculate that there is an ethnic predilection for multiple myeloma among Jewish populations, and this would explain the lack of significant difference between the Gaucher cohort and the population control group.

The association of Gaucher disease with polyclonal and monoclonal gammopathies has also been previously documented [22]: incidence of polyclonal gammopathies in adult enzyme-treated and untreated patients with type I Gaucher disease ranged between 14–25% among, whereas that of monoclonal gammopathies was 1% [31]. This latter incidence is dramatically lower than 17% (11/63) reported in the Dutch cohort [30]. Enzyme therapy apparently reduces polyclonal gammopathies, implying an association between polyclonal increases and Gaucher disease, but monoclonal gammopathies were unaffected by enzyme replacement [31].

It has been speculated that malignancy in Gaucher disease is due to chronic stimulation of the immune system by stored glycolipid, inducing lymphoproliferation [10,32–36]. Indeed, diffuse hyperglobulinemia has been noted in Gaucher disease as well as increased concurrence of monoclonal gammopathies [8,15,16,18]. Ferritin release by Gaucher cells may reduce T-cell function [36]; and serum from patients with Gaucher disease inhibits T-cell function and IgM release from B-cells [35]. These latter findings are corroborated by studies of increased levels of interleukin-6 [35], important signaling agents for proliferation in multiple myeloma [36] that are also significantly increased in Gaucher disease [35].

In conclusion, in a historical prospective cohort study of 500 type I patients relative to national data, the overall incidence of cancer and of hematological malignancies in particular is well within predicted rates. Therefore, further investigation of correlations with disease severity was discontinued. However, it should be noted that, despite the young age of the cohort, 20 cancers were noted. Too, rates of multiple myeloma may suggest a causal relationship. While patients' fears may be allayed, considering the size of this study population, it behooves treating physicians to closely follow patients with known risk factors such as monoclonal gammopathies, paraproteinuria, and other signs of plasma cell dyscrasia, particularly in those in whom osteolytic bone disease is a prominent feature.

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