Gaucher disease type I: associated morbidities and long term efficacy of enzyme replacement therapy

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Increased incidence of cancer in adult Gaucher disease in Western Europe

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Abstract

The adult form of Gaucher disease (type I GD) is associated with a high prevalence of hypergammaglobulinemia and monoclonal gammopathy of undetermined significance (MGUS). A significantly increased risk of cancer, especially of haematological types, has been found in Ashkenazi-Jewish GD type 1 patients.

In this study, incidence and mortality of cancer were assessed in a total of 131 GD patients of mixed ancestry in a population from Western Europe, i.e. 2 Gaucher referral centres in Germany (Düsseldorf) and the Netherlands (Amsterdam). Standardized rate ratios were determined by indirect standardisation, using age- and sex-specific incidence and mortality rates of the Dutch population. A total of 14 GD patients of non-Ashkenazi Jewish descent were identified of whom 5 had a hematologic malignancy. These numbers correspond to an increased risk of cancer of 2.5 (95% CI 1.1-4.7) and an increased risk of hematologic cancer of 12.7 (95% CI 2.6-37.0) among GD patients compared to the general population. In particular, the incidences of multiple myeloma and hepatocellular carcinoma in absence of pre-existing cirrhosis were highly elevated, with standardized rate ratios of 51.1 and 141.3, respectively. These strongly increased risks on developing cancer suggest that measures for early detection and prevention of hematological and hepatic malignancies in patients with Gaucher type I disease are mandatory.
Introduction

Gaucher disease (GD) is the most common of the lysosomal storage disorders and characterized by a deficiency of the lysosomal enzyme glucocerebrosidase (glucosylceramidase), which leads to the accumulation of glucocerebroside in macrophages1,2. Based upon the presence or absence of neurological symptoms, GD can be divided into three phenotypes; type 1 (non-neuronopathic), type 2 (acute neuronopathic) and type 3 (subacute neuronopathic). Type 1 GD is by far the most common form, accounting for 99% of the Gaucher cases. Numerous case reports have documented the occurrence of malignancies in GD. Particularly B-cell or plasma cell malignancies, such as multiple myeloma, leukaemia and lymphoma have been described. Also AL amyloidosis, a disorder arising from B-cell proliferation, has been reported in association with GD3-19. In relation to B-cell malignancies, a remarkably high prevalence of immunoglobulin abnormalities is associated with type I GD. The most common finding is hypergammaglobulinemia, but monoclonal gammapathy of undetermined significance (MGUS), a premalignant disorder that occasionally progresses to a multiple myeloma, lymphoma or CLL, is clearly more prevalent in GD20-24. Thus far, there has been only one publication on the risk of developing cancer for GD patients25. A significantly increased risk of cancer, especially of haematological type, was found for Ashkenazi Jewish GD type 1 patients. However, it has not been investigated whether cancer morbidity or mortality is also increased in GD patients of mixed ancestry, being mainly of non-Ashkenazi Jewish descent, a group of patients that encompasses a large part of the Gaucher population in Western Europe. Therefore, the type, incidence and mortality of cancer in 131 GD type 1 patients, a combined cohort from two Gaucher-referral centres in Germany and the Netherlands were investigated. In addition, the prevalence of the pre-malignant disorder MGUS was studied. The data show an increased incidence of cancer, especially of multiple myeloma and hepatocellular carcinoma (HCC). HCC-associated mortality was also significantly elevated.

Methods

Patients

The files of all patients with GD type I followed at the national referral centre for GD at the Academic Medical Centre (AMC), Amsterdam, the Netherlands, (n=63) or at the Heinrich Heine University Hospital (HHU), Düsseldorf, Germany, (n=80) during the years 1991-2003, were reviewed. Only patients, who had visited the clinic at least twice were included (n=63 for AMC, n=68 for HHU). The diagnosis of GD was based on the measurement of deficient glucocerebrosidase activity in leukocytes and genotyping26,27. Data on age, sex, splenectomy, genotype, occurrence and types of cancer since birth, age at diagnosis of GD and cancer, and date and cause of death were collected (Table I).
Severity Score Index (SSI) at start of therapy or at the first hospital visit was determined as described by Zimran. The presence and immunoglobulin-class of MGUS was determined in all Dutch patients and in 56 of 68 German patients, of whom these data were available. MGUS was defined as the presence of a serum monoclonal component (as determined by serum protein electrophoresis and immunofixation) at a concentration of < 30 g/L for IgG or < 20 g/L for IgA, < 1 g/24 h Bence Jones protein in urine, normal serum calcium and albumin and the absence of osteolytic lesions. No bone marrow examinations were performed.

**Indirect standardisation**

As Düsseldorf is located only 40 km from the Dutch border and no systematic German cancer rates are accessible, the Dutch national statistics were also applied to the German data. Incidence and mortality of cancer in the GD cohort were compared to the age- and sex-specific incidence and mortality rates of cancer, both overall and cause-specific, in the Dutch population as a whole in 1998, using indirect standardisation for five-year intervals. Patients were considered at risk for cancer starting at the date of the first visit to the respective hospitals, making it possible to verify the presence or absence of cancer in the medical files of the patients, thereby excluding the risk of overlooking a previously diagnosed cancer. The period at risk ended at the closing date of the study (1-1-2003), the date of death or the date of the last hospital visit, whichever came first. This also applied to patients with a diagnosis of cancer, who were considered to be at risk for developing another malignancy, and were not excluded from the period at risk unless they died or otherwise reached the end of the study period. For each of the five-year intervals, the expected number of malignancies and cancer-related deaths was calculated as the product of person years at risk and incidence or mortality rates, respectively. A malignancy was included as an observed case only in patients who were diagnosed with cancer during the period at risk (Table 2: # 1-6, 11-13). Standardized (morbidity-) Rate Ratios (SRR) and Standardized Mortality Ratio’s (SMR) were calculated as the ratio of observed cases to expected numbers. 95% confidence intervals (95% CI) for the SRR or SMR presuming a Poisson distribution for the observed numbers were determined.

**Statistics**

Characteristics of the Dutch and German patient population are presented as median and range. Differences between both study groups and between patients with and without cancer were tested either by Mann-Whitney test, Chi-squared test or Fisher’s exact test.
Results

Patients

The characteristics of the patients with Gaucher disease type I are presented in Table I. There were no significant differences in age, gender, number of splenectomies, SSI, genotype, number of cancer cases or cancer-related deaths between both centres. Less than 10% of the patients were known to be of Ashkenazi-Jewish ancestry. Patients in the Dutch patient group accounted for a total of 468 person years, the German patients for 181 person years. The lower number of patient years in the German subpopulation as compared to the Dutch population is based on two facts; first, a high number of new patients in the years 2000-2003 and second, the fact that referral of individual Gaucher patients in Germany to a centre, in contrast to the Netherlands, is not strictly regulated, resulting in significantly less follow-up visits in this population.

Subanalysis showed that 10/63 of the Dutch patients (16%) and 5 of the 56 (9%) German patients, met the criteria of MGUS. Eleven patients had a monoclonal protein, 3 had a biclonal protein and 1 had a triclonal protein.

<table>
<thead>
<tr>
<th></th>
<th>AMC</th>
<th>HHU</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>63</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Age in 2003 or at death (median, range)</td>
<td>48 (21-79)</td>
<td>49 (22-82)</td>
<td>NS</td>
</tr>
<tr>
<td>No of male patients (%)</td>
<td>32 (51)</td>
<td>33 (49)</td>
<td>NS</td>
</tr>
<tr>
<td>No of splenectomies (%)</td>
<td>23 (37)</td>
<td>19 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>SSI (median, range)</td>
<td>8 (3-19)</td>
<td>7 (2-16)</td>
<td>NS</td>
</tr>
<tr>
<td>No of patients with cancer (%)</td>
<td>9 (14)</td>
<td>5 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>No of cancer-related deaths (%)</td>
<td>3 (5)</td>
<td>2 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>No of patients with MGUS (%)</td>
<td>10 (16%)</td>
<td>5 (9%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table I. Characteristics of the study populations from Amsterdam (AMC) and Düsseldorf (HHU). Data reflect absolute numbers (and percentage) or median (and range) of the data from the respective cohorts. Abbreviations: AMC, Academic Medical Centre, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Düsseldorf; SSI, Severity score index; NS, not significant; ND, not determined.

The characteristics of the 14 Gaucher patients from both centres who were diagnosed with a malignancy are listed in Table II. Five of the 14 cases of cancer were of haematological type (2 multiple myelomas, one acute myeloid leukaemia, one B-cell lymphoma and one MALT lymphoma). Two patients (#3 and #5) were diagnosed with hepatocellular carcinoma (HCC). Both of these patients had no evidence of preexisting cirrhosis, either by chronic hepatitis, alcohol or nonalcoholic steatohepatitis (NASH). Patient #3 has been described previously in more detail 30. The median age at which cancer was diagnosed was 52 years (range 10-76). Seven of the fourteen patients with cancer died, in five of these cancer was identified as the cause of death (#1, #3, #5, #10 and #12).
There were no significant differences in gender, number of splenectomies, SSI, or genotype between the 14 patients with cancer and the 117 patients without cancer. The patients with cancer (both alive and dead) had a median age of 63 (range 38-80), which was significantly higher than the ones without (median 48, range 21-82, P=0.018). The median age at death of the patients with cancer was 72 (40-80).

Table III shows the observed and expected number of new cases of cancer and cancer-related deaths and the respective SRR’s and SMR’s. A significantly increased risk was found in the study population for all types of cancer (2.5; 95% CI 1.1-4.7), for haematological cancers as a whole (12.7; 95% CI 2.6-37.0), for multiple myeloma (51.1; 95% CI 6.2-184), and for hepatocellular carcinoma (141.3; 95% CI 17.1-510.5). Cancer-related mortality rates for all malignancies, as well as for haematological malignancies in general or multiple myeloma in particular, were increased but did not reach statistical significance. The SMR of dying from hepatocellular carcinoma was calculated to be 101.4, which was, despite the low number of cases, statistically significant.

**Table II. Characteristics of patients with Gaucher disease type I and cancer.** Patient-specific descriptive parameters are listed. Abbreviations: AMC, Academic Medical Centre, Amsterdam; HHU, hospital of the Heinrich-Heine-University, Düsseldorf; Sx, splenectomy; EST, enzyme supplementation therapy; HCC, hepatocellular carcinoma; MM, multiple myeloma; AML, acute myeloid leukemia

**Incidence of cancer is increased in GD**

Table III shows the observed and expected number of new cases of cancer and cancer-related deaths and the respective SRR’s and SMR’s. A significantly increased risk was found in the study population for all types of cancer (2.5; 95% CI 1.1-4.7), for haematological cancers as a whole (12.7; 95% CI 2.6-37.0), for multiple myeloma (51.1; 95% CI 6.2-184), and for hepatocellular carcinoma (141.3; 95% CI 17.1-510.5). Cancer-related mortality rates for all malignancies, as well as for haematological malignancies in general or multiple myeloma in particular, were increased but did not reach statistical significance. The SMR of dying from hepatocellular carcinoma was calculated to be 101.4, which was, despite the low number of cases, statistically significant.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type</th>
<th>Observed</th>
<th>Expected</th>
<th>SRR/SMR</th>
<th>95% CI of SRR/SMR</th>
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</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>All cancers</td>
<td>9</td>
<td>3.63</td>
<td>2.5</td>
<td>1.1-4.7*</td>
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<tr>
<td>Incidence</td>
<td>Haematological cancers</td>
<td>3</td>
<td>0.24</td>
<td>12.7</td>
<td>2.6-37.0*</td>
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<tr>
<td>Incidence</td>
<td>Multiple Myeloma</td>
<td>2</td>
<td>0.04</td>
<td>51.1</td>
<td>6.2-184*</td>
</tr>
<tr>
<td>Incidence</td>
<td>Hepatocellular carcinoma</td>
<td>2</td>
<td>0.01</td>
<td>141.3</td>
<td>17.1-510.5*</td>
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<tr>
<td>Mortality</td>
<td>All cancers</td>
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<td>1.69</td>
<td>3.0</td>
<td>0.96-6.9</td>
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<tr>
<td>Mortality</td>
<td>Haematological cancers</td>
<td>1</td>
<td>0.13</td>
<td>7.6</td>
<td>0.2-42.6</td>
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<tr>
<td>Mortality</td>
<td>Multiple Myeloma</td>
<td>1</td>
<td>0.03</td>
<td>36.3</td>
<td>0.9-202.0</td>
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<tr>
<td>Mortality</td>
<td>Hepatocellular carcinoma</td>
<td>2</td>
<td>0.02</td>
<td>101.4</td>
<td>12.3-366.1*</td>
</tr>
</tbody>
</table>

Table III. Incidence and mortality of cancer in GD patients. Incidence rates and mortality rates were obtained by comparison of the GD cohort with data from a representative non-GD Western-European population. Data were stratified into incidence and mortality and given as absolute numbers, Standardized Rate Ratio (SRR) or Standardized Mortality Ratio (SMR) and their respective 95% confidence intervals (95% CI). * signifies p< 0.05

Discussion

Using pooled data of 131 Gaucher type I patients from both the Netherlands and Germany, it was found that GD patients of non-Ashkenazi Jewish descent had a significantly increased risk of 2.5 for developing cancer. The risk of developing a hepatocellular carcinoma or a haematological malignancy, in particular multiple myeloma, was especially high (SRR 141.3, 12.7 and 51.1, respectively). This high risk for multiple myeloma is supported by the increased prevalence of MGUS (9% and 16% in the respective populations) The prevalence of MGUS in a population of similar age is estimated to be 1-2% [31-33]. There was no significant increase in total cancer-related mortality, with the exception of mortality caused by hepatocellular carcinoma, which was strongly elevated (SMR 101.4).

The standardized rate ratios for developing cancer found in this study were comparable to the ones from a previous study in which 48 Ashkenazi-Jewish Gaucher patients were compared to 511 control subjects from the same community [25]. Standardized rate ratios of 3.6 for developing cancer and of 14.7 for cancers of haematological type were found. With the present study it was established that the increased risk of cancer does not only apply to Gaucher patients of this specific ethnic origin, but also to the mixed population that is seen in Gaucher clinics in Western Europe. In addition, it was found that the risks of developing multiple myeloma or hepatocellular carcinoma are high.

In this study cancer-related mortality in GD patients was calculated. A strong increase in mortality due to hepatocellular carcinoma was found, but no significant increase in mortality due to cancer in general, to haematological malignancies, or to multiple myeloma could be shown. It should be noted however that for the combined cases and for multiple myeloma, the CI came close to a significant level (95% CI: 0.96-6.9 and 0.92-202.0, respectively) and that all the patients in our cohort who died, suffered from cancer, even if this was not the direct cause of death. Nevertheless, it is remarkable that the increased cancer morbidity we found is not associated with increased cancer mortality. One possible explanation could
be that the regular visits to a doctor lead to a greater chance of diagnosing cancer in an early stage, giving better opportunities for treatment. The results we found are in contrast with the previously mentioned study in which a statistically significant relative risk of 4.9 was found²⁵. However, in this study, mortality in patients with GD and cancer was studied, irrespective of the exact cause of death, taking into account also those patients with cancer who died of a different cause.

When studying the occurrence or mortality of a certain disease in a specific population, the type of control group is crucial. For the Netherlands, detailed age and sex specific incidence rates of all types of malignancies are available²⁹. By using these statistics in our comparison, the Dutch population as a whole served as a control group. Since there is currently no complete and detailed cancer registry for Germany, the Dutch national statistics were also applied to the German patients. The geographical proximity and the similarity of the Dutch and the German study population led us to believe these numbers would also provide the best possible control data for the German patients. The method of indirect standardisation precludes a selection bias of the control group, and corrects for age, sex and follow-up time, yielding an accurate risk estimate for this kind of survey. Moreover, we defined the number of years at risk as the time period during which patients visited our clinics on a regular basis, making it possible to verify the presence or absence of cancer in the medical files of the patients, ruling out the risk of overlooking a malignancy that was diagnosed in the past.

Although the population from Germany and the Netherlands were comparable with respect to age and overall severity as indicated by SSI, there was a higher number of cancer patients in the Dutch population. However, this difference disappears when correcting for the higher number of person years of the Dutch population.

The median age at which cancer was acquired was 52. This relatively young age could be attributed to the age distribution of our cohort, considering that 75% of the patients were younger than 60. The Gaucher patients with a history of cancer were relatively older than the ones without. Since no difference in disease severity or spleen status was apparent, the increased incidence in older patients is probably reflecting the expected course during ageing rather than referring to the severity of GD itself. We found no difference in GD genotype in patients with or without cancer. This makes a genotypic difference unlikely.

Of the 14 cases of cancer, 5 were of haematological type. In accordance with this high frequency, we found a particularly elevated SRR of developing a haematological malignancy and of developing multiple myeloma. Nine and 16% of the German and Dutch GD patients had an MGUS, a disorder that has the potential to progress to a multiple myeloma, lymphoma or CLL. Although national statistics on incidence of MGUS lack, studies have shown the prevalence of MGUS in a population of similar age to be 1-2%³¹-³³, which is considerably lower than what we found in our GD cohort.

The pathogenesis of these disorders in relation to GD remains obscure. Hypotheses have mainly concentrated on the presence of chronic antigenic stimulation of the B-cell
repertoire, resulting in hypergammaglobulinemia which may eventually transform into a B-cell malignancy\textsuperscript{21-23}. This antigenic stimulation is suggested to be due to accumulated lipid. Elevated levels of IL-6 and IL-10, cytokines that influence growth and differentiation of B-cells, as well as elevated levels of IL-8, which is chemotactic to B-cells, have been found in sera from patients with Gaucher disease\textsuperscript{34-36}. A recently developed glucocerebrosidase-deficient mouse showed evidence of B-cell proliferation, as well as elevated serum IgG levels\textsuperscript{37}. Immunological dysfunction has also been demonstrated in other parts of the immune system. Defective T-cell function was found in five patients with Gaucher disease, as shown by a reduction of E-rosetting capacity, probably resulting from elevated levels of ferritin released from Gaucher cells\textsuperscript{38}. Pollack et al suggested that serum from GD patients inhibits T-cell proliferation and B-cell immunoglobulin M secretion, probably through a factor released from monocytes\textsuperscript{39}.

Two of the patients with cancer had a hepatocellular carcinoma (HCC). One of these (patient #3) has been described previously\textsuperscript{30}. This patient had no risk factors for HCC (such as chronic hepatitis B or C) and no evidence of preexisting cirrhosis and had received enzyme supplementation therapy with alglucerase for the 9 months prior to diagnosis. A second report has described HCC in a Gaucher disease patient, who also had liver cirrhosis and hepatitis B\textsuperscript{40}. Both diseases were suggested as possible causative factors for the malignancy. Patient #5 from our study, who also had a HCC, had received radiotherapy on the liver and spleen as an obsolete therapy for GD, at the age of 20. She did not have hepatitis B or C and had used alglucerase during 5 years. All patients were splenectomized and had gross hepatomegaly. It is likely that GD with advanced hepatic involvement after splenectomy, including fibrosis, is related to the occurrence of HCC.

The data from this study show that Gaucher patients of mixed ancestry, mostly non-Ashkenazi-Jewish, have a significantly increased risk for developing cancer, in particular of multiple myeloma and hepatocellular carcinoma. Physicians taking care of Gaucher patients should be aware of these risks and simple diagnostic tests that can be used to detect a multiple myeloma or hepatocellular carcinoma, such as quantification of immunoglobulins, serum electrophoresis and immunofixation and serum \(\alpha\)-fetoprotein respectively. We recommend to perform these tests on a yearly basis, in line with recommendations for patients with MGUS or hepatitis B carriers\textsuperscript{41}.

Reference List

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