Decreased salivary output in patients with Gaucher disease

B. DAYAN1, D. ELSTEIN1, A. ZIMRAN1,2 and G. NESHER2

From the 1Gaucher Clinic and 2Department of Medicine, Shaare Zedek Medical Center, Jerusalem, Israel

Received 7 June 2002 and in revised form 9 September 2002

Summary

Background: Gaucher disease, the most common sphingolipid storage disease, results in accumulation of glucocerebroside in macrophages or ‘Gaucher cells’. In a preliminary screening of 109 patients with type I disease, when asked specifically about dry mouth, approximately one quarter claimed to suffer from this symptom.

Aim: To ascertain whether decreased salivary output is a feature of Gaucher disease.

Design: Prospective case-control study.

Methods: Salivary output was measured in 65 adult patients and 65 healthy controls using the Saxon test with Hochberg’s modification.

Results: Mean salivary output was 1.91 ± 1.19 g/min in the patient group vs. 2.74 ± 1.17 g/min in the control group (p<0.001). This difference was greater among males. These results were not improved in the patients receiving enzyme replacement therapy, which is effective in ameliorating most Gaucher-related signs and symptoms.

Discussion: Recent studies have implicated an association between sicca syndrome and viral hepatitis C infection, which may imply an immunological trigger for these findings, but in this specific cohort, only three patients were reactive for hepatitis C. Follow-up of patients, both untreated and receiving enzyme therapy, is needed to delineate the association with salivary hypofunction, and ascertain whether enzyme therapy may induce sicca symptoms.

Introduction

Gaucher disease, the most common sphingolipid storage disease, is an autosomal recessive disorder caused by mutations in the beta-glucocerebrosidase gene leading to deficient activity of this lysosomal enzyme. The resulting accumulation of glucocerebroside is primarily in macrophages, giving rise to foam cells or ‘Gaucher cells’.1

There are two neuronopathic forms of the disease (types II and III), but type I, the non-neuronopathic form, is the most common, and although panethnic, 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. However, most patients with the most common genotype, N370S/N370S, especially Ashkenazi Jews, have mild disease or are even asymptomatic.3

With the advent of enzyme replacement therapy more than a decade ago,4 patients with symptomatic disease were able to benefit from safe and effective treatment that invariably reduced hepatosplenomegaly and improved haematological features, as well as ameliorating bone pains and preventing skeletal complications.

As the number of patients brought to medical attention has increased, particularly in large referral
clinics, awareness of less common features of Gaucher disease has been appreciated. Thus, it was noted that some patients complain of a dry-mouth feeling. In a preliminary screening of 109 patients with type I disease, when asked specifically about dry mouth, approximately one quarter claimed to suffer from this symptom. Sicca symptoms and salivary gland involvement have never been reported in Gaucher disease. Thus, the aim of this study was to evaluate the prevalence of the ‘dry mouth’ phenomenon in patients with Gaucher disease compared to controls, using an objective method of determining the salivary output, since subjective feelings of dry mouth do not necessarily correlate with decreased salivary output.5

Methods

Sixty-five adult patients of Ashkenazic Jewish descent with type 1 Gaucher disease who were followed at the Gaucher Clinic, and who agreed to participate, were included in this study; 65 normal healthy adults of Ashkenazic Jewish descent were used as controls. In all patients, Gaucher disease was diagnosed by enzyme assay and confirmed by molecular analysis. The severity of Gaucher disease was evaluated by the severity score index (SSI) at presentation.6 The presence of anti-nuclear antibodies (ANA) was determined by indirect immunofluorescence, with titres of 1:40 or greater considered positive. None of the patients nor the controls was on medications that could affect salivary output. None had had radiation therapy or had undergone surgery of the head or neck.

Salivary output was measured in patients and controls using the Saxon test7 with Hochberg’s modification.8 Briefly, a folded 10 × 10 cm gauze pad was chewed for one minute. The gauze pads were weighed individually on analytical scales prior to and directly after chewing; the difference in weight was calculated as salivary output. The precision of the scale was 0.1 mg. The cutoff line between normal and low output (i.e. xerostomia) was set at the lowest 10th percentile of the control group’s values.8

Statistical analysis

As the salivary output in patients with Gaucher disease was not normally distributed, non-parametric methods including χ² analysis of contingency tables, Mann-Whitney rank-sum test, and Spearman rank correlation, were used to ascertain statistical significance.

Results

The male:female ratios of the patients and the controls were 34:31 and 30:35, respectively. The mean age of the patients was 41.1 ± 14.9 years; that of the controls was 37.1 ± 14.6 years. These differences were not statistically significant.

Salivary output in the patients group was skewed to the left (Figure 1) whereas salivary output in the control group was normally distributed. The mean salivary output in the patients group was 1.91 ± 1.19 g/min relative to 2.74 ± 1.17 g/min in the control group (p < 0.001). This difference was greater among males (Table 1).

The cutoff point between normal and low salivary output was 1.13 g/min (the lowest 10th percentile of the control group’s values). The respective cutoff values for the subgroups of males and females were 1.22 and 1.06 g/min. Low output was measured in 35.4% of the patients, relative to 10.8% of the control group (p = 0.002). When the subgroups of males and females were compared

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salivary output</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1.86 ± 1.29</td>
<td>3.03 ± 1.24</td>
<td>0.001</td>
</tr>
<tr>
<td>Females</td>
<td>1.94 ± 1.07</td>
<td>2.49 ± 1.06</td>
<td>0.05</td>
</tr>
<tr>
<td>All</td>
<td>1.91 ± 1.19</td>
<td>2.74 ± 1.17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Xerostomia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>13 (38.2%)</td>
<td>3 (10%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Females</td>
<td>10 (32.3%)</td>
<td>4 (11.4%)</td>
<td>0.078</td>
</tr>
<tr>
<td>All</td>
<td>23 (35.4%)</td>
<td>7 (10.8%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Cut-off between normal and low salivary output was lowest 10th percentile of the control group’s values (see text).
Table 2  Saliva output in patients subdivided by Severity Score Index (SSI), and by treatment status with enzyme replacement therapy (ERT).

<table>
<thead>
<tr>
<th></th>
<th>Saliva output (g/min)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSI &lt;10</td>
<td>2.33 ± 1.28</td>
<td></td>
</tr>
<tr>
<td>SSI &gt;10</td>
<td>1.54 ± 0.93</td>
<td>0.011</td>
</tr>
<tr>
<td>ERT</td>
<td>1.77 ± 1.03</td>
<td></td>
</tr>
<tr>
<td>No ERT</td>
<td>2.08 ± 1.35</td>
<td>NS</td>
</tr>
</tbody>
</table>

...prevalence of dry mouth symptoms increased with age and was greater in women than in men, but this was not seen in the current study. On the other hand, in studies of patients with other diseases associated with sicca symptoms, such as systemic lupus erythematosus and rheumatoid arthritis, oral and ocular dryness were not correlated with output rates of saliva or tears, and there was no correlation with age or disease severity.

A recent series of studies has implicated an association between sicca syndrome and viral hepatitis C infection. In a study of patients with sicca symptoms, the prevalence of hepatitis C infection was 19%. Conversely, in a study of patients with hepatitis C infection, sicca syndrome was present in 62%; all patients had oral dryness and half of them also had ocular dryness.

The aetiology of xerostomia in patients with Gaucher disease is unclear. A possible explanation would be infiltration of Gaucher cells into the salivary glands, interfering with saliva production. The finding that decreased salivary output was associated with disease severity may support this view, but without histological examination, there is no means of confirming this hypothesis. Although the current study employed the Saxon test as a means of quantifying oral dryness, this test correlates well with the Schirmer test for tear secretion. Indeed, many patients with Gaucher disease also have complained of dry eyes. However, other factors that may effect dry mouth or eyes such as other medications, diet, lifestyle, etc. were not investigated.

One hypothetical construct that has previously been suggested is chronic stimulation of the immune system in Gaucher disease to explain the findings of elevated levels of pro-inflammatory cytokines and relatively higher incidences of lymphoproliferative disorders, plasma-cell dyscrasias and amyloidosis in Gaucher disease.

Alternatively, one may look for an immunological trigger, as hepatitis C viral infection or potentially consider that sicca symptoms are secondary to a specific manifestation of Gaucher disease such as abnormalities in liver function. With regard to the incidence of hepatitis C infection in this cohort, there were only three patients; nonetheless, since the incidence of hepatitis C infection in our referral clinic is higher, a larger series is warranted to investigate this possibility. As liver abnormality is a rather rare feature of Gaucher disease, and is mostly seen in patients with other signs of severe involvement (Zimran and Elstein, unpublished data), this may explain the inverse correlation between the results of the Saxon test and SSI scores.
Larger cohorts are required to further evaluate xerostomia and even xerophthalmia in patients with Gaucher disease. As the Saxon test is simple and inexpensive as well as being well validated as a measure of both dry mouth and dry eyes, this may be easy to accomplish among various populations of patients with Gaucher disease. Follow-up of patients receiving enzyme treatment should assess the effect on salivary hypofunction, or possibly investigate whether enzyme therapy per se induces an immunological stimulus that induces sicca symptoms, since there was a trend to decreased salivary production in treated patients.

Our recommendation would be that patients should be questioned as to the feeling of dry mouth and/or dry eyes. The Saxon test, however, should be more universally applied, and in patients with low salivary or lacrimal secretion, the use of saliva or tear substitutes may be considered.

References


