Scintigraphy of the salivary glands in Sjögren’s syndrome

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SUMMARY Scintigraphy of the salivary glands with technetium-sodium pertechnetate (99mTc) was undertaken on 320 patients with oral dryness or connective tissue disease using a computer assisted method that gave quantitative results about the major salivary gland function. Compared with clinical and histological data, scintigraphy provides a sensitive method, even though it is not specific, for detecting minimal injuries to salivary glands in patients suspected of having Sjögren’s syndrome. Moreover, it might differentiate between the Sjögren-like syndrome and the sequelae of radiotherapy in patients with bone marrow graft. Scintigraphy of the major salivary glands could therefore form part of the routine investigation of patients with Sjögren’s syndrome.

Sjögren’s syndrome is usually characterised by ocular disease and complaints of oral dryness. Xerostomia is difficult to assess when either complex sicca syndrome is not evident, or the clinical signs and symptoms of Sjögren’s syndrome are varied. Attempts have been made to develop diagnostic procedures that could determine the functional state of the salivary glands. Measurement of flow through the parotid gland entails a degree of risk, pain, and discomfort and cannot therefore be proposed as a routine technique. Sialography, which requires the introduction of a radio-opaque element into the parotid ductal system emphasises the morphological abnormalities but does not show the functional state of the salivary glands.

Scintigraphy of the major salivary glands based on the ability of the parotid and submandibular glands to trap technetium-sodium pertechnetate (99mTc) has been introduced to show the functional abnormalities of the salivary glands. This investigation aimed to study the potential of scintigraphy with a computer assisted method for use as a sensitive and non-invasive tool to measure the degree of impairment of the salivary glands in Sjögren’s syndrome and then to compare results with data obtained from labial gland biopsy.

Patients and methods

Over the past five years a total of 320 patients (233 females, 87 males, aged 7 to 80 (mean 49 years)) underwent scintigraphy of the salivary glands. Patients were either suspected of having isolated Sjögren’s syndrome (145 primary Sjögren’s syndrome) and were referred for clinical detection of the sicca syndrome or systematically underwent scintigraphy of the salivary glands because of autoimmune disease (165 secondary Sjögren’s syndrome), such as systemic lupus erythematosus, rheumatoid arthritis, scleroderma or chronic graft versus host disease (CGVHD). In addition, 10 patients had other problems such as salivary lithiasis or sarcoidosis, or sequelae from psychotropic drugs or radiotherapy for Hodgkin’s disease (table 1).

All patients were carefully questioned regarding oral or ocular dryness and clinically examined. Lower labial gland biopsy and histopathological grading of minor salivary glands disease were done according to the method of Chisholm and Mason or Greenspan. Sjögren’s syndrome was diagnosed according to the criteria defined by Kaplan.

For scintigraphy, 37 MBq/10 kg of 99mTc was administered intravenously to patients lying supine under a scintillation camera, their heads positioned relative to the camera crystals. Sequential scintiphotographs were taken at 10, 15, 30 and 35 minutes. After 20 minutes 1 mg pilocarpine was injected subcutaneously to obtain an intensive and rapid flow rate. This method of stimulating salivary flow is particularly effective and reproducible from one patient to another. The entire procedure did not take more than 40 minutes. The resulting data covered the
Table 1  Clinical data from 320 patients

| Complaints of oral or ocular dryness | 145 |
| Connective tissue disease | 165 |
| Bone marrow transplantation | 67 |
| Rheumatoid arthritis | 39 |
| Systemic lupus erythematosus | 20 |
| Scleroderma | 10 |
| Thrombocytopenic purpura | 7 |
| Chronic active hepatitis | 4 |
| Primary biliary cirrhosis | 3 |
| Necrotising vasculitides | 3 |
| Pernicious anaemia | 2 |
| Grave’s disease | 2 |
| Polymyositis | 2 |
| Mixed connective tissue disease | 2 |
| Febrile neutrophilic dermatosis | 1 |
| Polychondritis | 1 |
| Psoriatic arthritis | 1 |
| Human immunodeficiency virus infection | 1 |
| Other | 10 |
| Salivary lithiasis | 4 |
| Sarcoidosis | 3 |
| Psychotropic drugs | 2 |
| Radiotherapy | 1 |

four regions of interest of the major salivary glands (fig 1). In addition, two other regions of interest were chosen from vascular and oral areas; background, deducted from the vascular area, was subtracted from the activity recorded for each salivary gland. The computer (SOPHA) prepared a time curve with an ascending slope corresponding to the uptake by the salivary gland and with a descending slope corre-

Fig 1  Regions of interest shown by the computer procedure.

Fig 2  Uptake and emptying curves obtained from normal or impaired parotid glands.

responding to the excretion (fig 2). Two variables were then prepared: rate of excretion, expressed as %/minute, was obtained from the segment of the second part of the curve corresponding to excretion and showing maximal decrease in activity; and the ejection fraction of $^{99m}$Tc given in the formula: (1-remaining activity/maximal radioactivity, with this variable expressed in %). The uptake was less valid than the flow rate because normal salivary gland uptake was weak (<1%) compared with thyroid or gastric uptake. The ejection fraction of $^{99m}$Tc differed from mean rate of excretion and provided better data on the total amount of excretion.

As reported previously $^{10}$ mean rate of excretion values were classified into four grades of salivary gland impairment. The results were expressed either as the mean of the four glands or separately as a value of each parotid and submandibular gland (table 2). Grade I corresponded to normal mean rate of excretion values and grade IV to severe functional

Table 2  Classification of salivary impairment according to mean rate of excretion scintigraphic values

| Mean rate of excretion from major salivary glands as %/min: |
|------------------|------------------|
| Grade I | 26 ≤ mean rate of excretion |
| Grade II | 18 ≤ mean rate of excretion < 26 |
| Grade III | 10 ≤ mean rate of excretion < 18 |
| Grade IV | mean rate of excretion < 10 |

| Parotid mean rate of excretion: |
|------------------|------------------|
| Grade I | 32 ≤ mean rate of excretion |
| Grade II | 22 ≤ mean rate of excretion < 32 |
| Grade III | 12 ≤ mean rate of excretion < 22 |
| Grade IV | mean rate of excretion < 12 |

| Submandibular mean rate of excretion: |
|------------------|------------------|
| Grade I | 20 ≤ mean rate of excretion |
| Grade II | 13.5 ≤ mean rate of excretion < 20 |
| Grade III | 7 ≤ mean rate of excretion < 13.5 |
| Grade IV | mean rate of excretion < 7 |
impairment of salivary glands. A few minutes after injection of pilocarpine normal results corresponded to a disappearance of more than 80% of the recorded isotope activity of salivary glands. In contrast, in cases of salivary dysfunction $^{99m}$Tc was still localised in the glands 20 minutes after injection of pilocarpine. In addition, differences were found in the results for mean rate of excretion between the parotid and submandibular glands, and such differences were only accounted for when higher than 8%. Moreover, asymmetrical results were considered to be abnormal above a difference of more than 5% (fig 3).

The computer package used is a comprehensive unit consisting of 10 macrofunctions using 20 programs, offering nine functions including research selection, acquisition, file control, file rotation, subtraction of the thyroid area, curve plotting, mathematical computation, curve display and copy print. Each function must also take into consideration any difficulty incurred during image processing. For example, acquired images may not be correctly oriented and this justifies the file rotation function. In addition, the cine mode function is required to check on the complete immobilisation of patients during the scan. As special attention has been given in this package to correct any errors of handling, acquisition need not be repeated.

### Results

The mean rate of excretion was abnormal in 284 and normal in 36 patients. Table 3 shows the results of scintigraphy of submandibular and parotid glands according to the classification of mean rate of excretion. These results, taking into account the clinical and histological data, allowed a final diagnosis to be made (table 4).

Our cases included 131 cases of isolated Sjögren's syndrome and 143 cases of secondary Sjögren's syndrome related to either accompanying autoimmune disease (n = 84) or bone marrow transplant (n = 59). Of the 145 patients referred for complaints of oral or ocular dryness, primary Sjögren's syndrome was diagnosed in 131 cases; 14 had normal scintigrams. All grafted patients had eight had abnormal scintigrams and were then regarded as secondary Sjögren's syndrome (n = 59); 84 patients with autoimmune disease were also classified as secondary Sjögren's syndrome.

Grafted patients were normally grade III or IV in our classification, which indicates a severe impairment of salivary glands, either as a result of radiotherapy or a Sjögren-like syndrome, an early indication of CGVHD. Discrepancies between submandibular and parotid mean rate of excretion values were observed in 50% of grafted patients, especially after radiotherapy, but patients with CGVHD showed homogeneous impairment of salivary glands.

Correlation between mean rate of excretion value and clinical, biological, or histological data was significant (table 5), especially in patients with grade III or IV disease. Discrepancies existed between the

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<th>Results according to mean rate of excretion classification</th>
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<td>Homogeneous results between submandibular and parotid glands (n = 189)</td>
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<tr>
<td>Grade of mean rate of excretion</td>
<td>I</td>
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<tr>
<td>---</td>
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</tr>
<tr>
<td>Normal scintigraphy</td>
<td>31</td>
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<table>
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<th>Table 4</th>
<th>Results observed in 320 patients</th>
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<td>Abnormal scintigraphy</td>
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<tr>
<td>Primary Sjögren's syndrome</td>
<td>131</td>
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<tr>
<td>Secondary Sjögren's syndrome</td>
<td>143</td>
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<tr>
<td>CGVHD or radiotherapy</td>
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<tr>
<td>Autoimmune disease</td>
<td>84</td>
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parotid and submandibular glands in five of the 36 patients initially considered to be "normal" in terms of the mean rate of excretion value. In some cases the submandibular glands were abnormal and the parotid glands normal; in other cases the converse was true. Such discrepancies must be taken into account, especially in grades I and II corresponding to phases in which subjective complaints of oral dryness are generally low and the histology of salivary glands negative. These discrepancies generally precede clinical or histological manifestations. In such cases scintigraphic monitoring is recommended.

Discussion

The main aim of scintigraphy of the salivary glands with 99mTc in patients with subjective complaints of oral dryness is to ascertain the oral component affected. An accurate functional and quantitative study of the salivary gland dysfunction is supplied by the computer assisted method.

Evaluation of morphological salivary abnormalities does not provide any additional information in patients with Sjögren's syndrome. Entrapment of 99mTc in the salivary glands may be normal or slightly decreased. The most important data are the failure of parotid or submandibular glands, or both, to empty in response to pilocarpine. In Sjögren's syndrome the salivary functional impairment is shown by decreased mean rate of excretion values. Results of scintigraphy expressed by mean rate of excretion are more suitable than methods which emphasise the amount of 99mTc uptake, as only 0.4-0.6% of 99mTc is trapped by the salivary glands.11

Stimulation of parasympathetic activity, mimicked by the effects of pilocarpine, produces a profuse watery salivary flow and reduces the duration of the procedure (40 minutes). It emphasises the functional salivary impairment, which is of great importance in the early stages of salivary gland disease.

The close correlation between clinical manifestations and scintigraphy indicates that salivary imaging is a suitable procedure which agrees with the findings published by others12-17 for assessing oral dryness. This is especially true in patients with other autoimmune diseases, although patients did not complain about oral dryness at the time of scintigraphy.

Discrepancies between the results of parotid and submandibular mean rate of excretion values are of special interest when the mean rate of excretion was considered as grade I (normal) or grade II (slightly impaired). Table 3 shows that 31 patients had homogeneous results but 26 patients had normal parotid mean rate of excretion values (grade I) but abnormal grade II submandibular disease; conversely, 13 patients had normal submandibular mean rate of excretion values and abnormal grade II parotid disease.

These results show that a "normal" mean rate of excretion value takes into account results from parotid and submandibular glands, therefore attention must be given to the mean rate of excretion values of parotid and submandibular glands. Indeed, some Sjögren’s syndrome patients in the early stages of salivary gland impairment, have either parotid or submandibular injuries shown by scintigraphy. Unexpectedly, a slight impairment of submandibular gland function shown by scintigraphy, in the presence of normal parotid mean rate of excretion values, suggests that the submandibular glands are the more reliable variable of salivary gland disease in Sjögren’s syndrome.7 Moreover, discrepancies between parotid and submandibular mean rate of excretion values are more often observed in patients with bone marrow graft and radiotherapy sequelae compared with patients with CGVHD. Scintigraphy could therefore differentiate Sjögren-like syndrome presenting as an early stage of CGVHD18 from oral dryness secondary to radiotherapy in grafted patients. These results should be taken into account prior to management of the patient.

Despite the correlation obtained between scintigraphy and the results of labial gland biopsy, discrepancies have been observed. There are several explanations: lymphocytic infiltration is usually observed before overt salivary glands disease; scintigraphy provides functional data on the major salivary gland disease whereas labial gland biopsy only concerns minor salivary glands; 99mTc is trapped in ducts whereas the early histological salivary gland impairment is in the acinar cells; samples are too small; minor salivary glands become affected at a later stage than parotid and submandibular glands.

In conclusion, salivary scintigraphy seems to be a very sensitive tool for detecting the early states of salivary gland impairment observed in Sjögren’s syndrome and other autoimmune disorders.

<table>
<thead>
<tr>
<th>Complaints of oral or ocular dryness</th>
<th>Clinical</th>
<th>Histological</th>
<th>Scintigraphic</th>
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<tr>
<td>Presence</td>
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<td>105</td>
<td>131</td>
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<tr>
<td>Absence</td>
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<td>40</td>
<td>14</td>
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<tr>
<td>Connective tissue disease</td>
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<td></td>
<td></td>
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<tr>
<td>Presence</td>
<td>165</td>
<td>123</td>
<td>143</td>
</tr>
<tr>
<td>Absence</td>
<td>0</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
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References


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