EVIDENCE OF CEREBRAL HYPOPERFUSION WITH ⁹⁹ᵐTc HMPAO SPECT IN EGYPTIAN SCLERODERMA PATIENTS

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KEY WORDS: ⁹⁹ᵐTc-Hexamethylpropyleneamine-Oxime (HMPAO), Single Photon Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI), Magnetic Resonance Angiography (MRA), Systemic Sclerosis (SSc), Regional Cerebral Blood Flow (rCBF).

ABSTRACT

Objective: The aim of this study was to investigate regional cerebral blood flow (rCBF) with ⁹⁹ᵐTc-hexamethylpropyleneamine oxine (HMPAO) single photon emission computed tomography (SPECT) in a group of 22 patients affected with systemic sclerosis (SSc). The SPECT findings were correlated with clinical data & MRI whenever possible.

Method: The study was conducted on 22 Egyptian SSc patients in comparison to ten healthy age-matched controls. Subjects affected with concomitant diseases that might interfere with the interpretation of the SPECT results were excluded. SPECT findings were correlated with clinical data, magnetic resonance imaging (MRI) of the brain and magnetic resonance angiography if available.

Results: Twelve SSc patients (54.5%) showed cerebral hypoperfusion, focal in 8 (66.7%) patients and diffuse hypoperfusion in 4 (33.3%) patients at the SPECT analysis. MRI was available in 15 patients and was shown to be altered in five of them (33.3%). Magnetic resonance angiography (MRA) was normal in those five patients except one. No significant differences were found between the group of SSc patients showing hypoperfusion and those showing a normal SPECT scan regarding age, the duration of disease and damage of other organs typically involved in the disease.

Conclusions: Focal or diffuse cerebral hypoperfusion was found with SPECT in more than half of the neurologically
asymptomatic SSc patients. SPECT was more sensitive in reflecting changes of cerebral blood flow than MRI. The hypoperfusion was not linked to ageing and possibly reflects the cerebral location of the microangiopathic process characterizing the disease.

INTRODUCTION

Scleroderma or systemic sclerosis (SSc) is a diffuse connective tissue disease characterized by proliferation of the vascular tissue, obliterative microvascular lesions and diffuse interstitial fibrosis. It is a multisystem disease and most case reports describing the effects of SSc on the nervous system have focused on the peripheral nervous system and the cranial nerves. The high incidence of cerebral disease originally reported in SSc patients was usually secondary to cardiopulmonary or renal disease (Gordon & Silverstein, 1970).

The microangiopathy of the brain therefore seems to be the main pathogenic marker, although macrovascular lesions have also been reported in SSc (Veale et al., 1995). However, some selected cases indicate that cerebral arteritis can occur at least in progressive SSc forms (Cutolo et al., 1995).

Heron et al. (1998) found extensive wall calcification of small arteries and arterioles in the brains of two autopsy scleroderma cases.

SPECT is a measure of brain perfusion. The advantages of SPECT are that it is non-invasive, it enables anatomic imaging of lesions and most important it is a means of functional imaging (Julie et al., 1995).

Aim Of Work

We investigated the possible early appearance of cerebral vascular involvement using $^{99m}$Tc-HMPAO SPECT to measure rCBF in 22 scleroderma patients and correlated them with clinical data and MRI of the brain whenever possible.

PATIENTS AND METHODS

This work was conducted on 22 definite SSc patients diagnosed according to the preliminary criteria of the American College of Rheumatology classification of systemic sclerosis (Masi et al., 1980). Patients were selected from the Outpatient Clinic of the Rheumatology and Rehabilitation Department, Ain Shams University Hospitals. Patients with either limited or diffuse cutaneous involvement were considered for inclusion in the study. Ten healthy age and sex-matched subjects served as a control group.
All patients were subjected to the following:

A full medical history taking including onset, course and duration of the disease and a thorough clinical examination with special emphasis on the extent of skin involvement; joint affection, chest and cardiac examination and neurological examination which help in the diagnosis and assessment of the severity of the disease. Exclusion criteria included severe or uncontrolled arterial hypertension, uncontrolled diabetes mellitus, as well as relevant renal, respiratory or hepatic failure and severe anemia.

Brain SPECT Technique:

Twenty-two patients and ten controls were subjected to steady state measurement of cerebral blood flow. Imaging commenced 20 min after IV injection of 13 m Ci (480 MBq) $^{99m}$Te-HMPAO. The imaging device was a single head rectangular Sophy XRT gamma camera mounted to parrel hole high resolution collimator and connected to on-line computer system. The camera head was allowed to rotate 360° around the patient's head with cantho-meatal line perpendicular to the camera surface at the anterior start point. Image acquisition was 64 frames through the entire 360 circular rotation. Images were reconstructed in the transverse, sagittal and coronal planes

Scan Interpretation:

All rCBF studies of patients and controls were examined by visual analysis. If there were more than 2 focal uptake defects in at least 2 consecutive slices, SPECT scan were classified as showing diffuse uptake defects (Rubbert et al., 1993).

MRI of 15 patients was available, it was performed using a 1.5-TMR unit GE Multisync LCD 2010 with echo-planar capability with the following parameters:

Sagittal T$_1$ - weighted spin – echo (500/12/1, 1: 20-minutes acquisition time), Axial T$_2$ weighted fast spin-echo (3000/82/1, 42-second acquisition time), and fluid-attenuated inversion recovery (FLAIR) (10002/162/1, 3: 20-min acquisition time) sequences; and MR using echo-planar techniques was performed for some selected patients.

Statistical analysis:

The clinical and radiological data were analyzed statistically using SPSS-under windows verion 6.21 to obtain:

Descriptive statistics:
The data were expressed as mean ± SD with the mathematical range (min. – max). Number (No.) and percent (%) for qualitative data.

**Analytical statistics:**

Comparison between two independent means by student's "t" test. CHI-square test for qualitative data as p values of < 0.05 were considered significant.

**RESULTS**

The patients group comprised 22 SSc patients. They were 2 (9%) males and 20 (91%) females. Their ages ranged from 19-65 years with a mean of 31.62±13.21 years and their disease duration ranged from 1-15 years with a mean of 5.23±5.13 years. Fourteen of patients (63.6%) had diffuse SSc, while eight (36.4%) had limited SSc according to the classification proposed by LeRoy et al. (1988).

The control group comprised 10 healthy subjects clinically free from any rheumatic, vascular or immunological disorders. They were 2 males (20%) and 8 females (80%). Their ages ranged from 22-55 years with a mean of 30.5 ± 9.45 years.

Table (1): The frequencies of clinical data of SSc patients.

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse SSc</td>
<td>14</td>
<td>63.6</td>
</tr>
<tr>
<td>Limited SSc</td>
<td>8</td>
<td>36.4</td>
</tr>
<tr>
<td>Raynaud's phenomenon</td>
<td>14</td>
<td>63.6</td>
</tr>
<tr>
<td>Sclerodactyl</td>
<td>15</td>
<td>68.2</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>6</td>
<td>27.3</td>
</tr>
<tr>
<td>Telangiectasia cutis</td>
<td>2</td>
<td>9.1</td>
</tr>
<tr>
<td>Arthralgia / arthritis</td>
<td>12</td>
<td>54.5</td>
</tr>
<tr>
<td>Esophageal dysesthesia</td>
<td>16</td>
<td>72.7</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Renal affection</td>
<td>6</td>
<td>27.3</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>5</td>
<td>22.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>22</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Out of the 22 SSc patients, Raynaud's phenomenon was found in 14 (63.6%), sclerodactyly in 15 (68.2%), digital ulcers in 6 (27.3%), telangiectasia cutis in 2 (9.1%), arthralgia or arthritis in 12 (54.5%), esophageal dysesthesia in 16 (72.7%), pulmonary involvement in the form of interstitial pulmonary fibrosis in 9 (41%), renal affection in 6 (27.3%) and peripheral neuropathy in 5 (22.7%) of them. There was neither cardiac nor muscular involvement in our patients (Table-1).
SPECT scan was performed on 22 patients and 10 controls:

All controls showed normal SPECT scan findings. SPECT scanning was abnormal in twelve SSc patients (54.5%). Focal hypoperfusion was found in 8 patients (66.7%), while diffuse hypoperfusion was found in 4 patients (33.3%). All patients with diffuse hypoperfusion were diffuse SSc while 3/8 (37.5%) with focal hypoperfusion were limited SSc. (Table-2).

Table (2): SPECT findings in 22 patients with diffuse and limited SSc.

<table>
<thead>
<tr>
<th>SPECT Results</th>
<th>Diffuse SSc</th>
<th>Limited SSc</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Focal uptake defects</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Diffuse uptake defects</td>
<td>4</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

The location of focal hypoperfusion was heterogeneous among patients. There was a small perfusion defect. Hypoperfusion in the frontal and parietal areas was found in 3 out of 8 (37.5%) patients, while a small defect in the occipital area was found in one patient (12.5%).

Diffuse hypoperfusion was found in the frontal, parietal and occipital lobes in 3/4 patients (75%). One patient (25%), in addition had perfusion defects of the cerebellum, basal ganglia and thalami.

MRI scan was available for 15 patients, all patients with abnormal SPECT scan and 3 patients with normal SPECT. MRI scan showed signal abnormalities in 5 out of 15 (33.3%) of SSc patients. The incidence was higher in patients with abnormal SPECT 5 out of 12 (41.7%).

Magnetic resonance angiography (MRA) revealed normal findings in 4 out of 5 patients at the major vascular supply of the internal carotid artery as well as basilar flow. MRA was positive in one patient, whose neurological examination revealed right hemiparesis and hemihyposthesia with exaggerated deep reflexes and extensor planter response.

No statistical significant difference (p>0.05) was found between patients with a normal SPECT scan and patients with hypoperfusion for age (patients with a normal scan, 48±12 years; patients with an abnormal scan, 51±9.7 or the duration of disease (patients with a normal scan, 7.6±4.3 years, patients with an abnormal scan, 7.9±4.1 years).

No statistical significant difference (p>0.05) was found between SPECT-positive and SPECT-negative patients as regards to clinical data and no relationship was observed.
DISCUSSION

Structural changes of the small arteries and arterioles (typically concentric fibrous intimal thickening) have been described in nearly every organ of systemic sclerosis patients (D'Angelo et al., 1969). Blood vessels would also be expected to be involved in the central nervous system, however pathological studies had failed to demonstrate primary cerebrovascular changes in SSc (Heron et al., 1998).

The present study showed that 54.5% of patients affected with SSc present focal or diffuse cerebral hypoperfusion as assessed with $^{99m}$Tc-HMPAO SPECT. These results confirm the findings that were obtained by the planar quantitative Xenon-133 clearance method (Nobili et al., 1997). Our results agreed with the previous study by Cutolo et al. (2000), which revealed 52% of SSc patients with cerebral hypoperfusion with SPECT.

SPECT findings are reported in nearly neurologically asymptomatic SSc patients. SPECT was shown to be very sensitive and disclose brain functional deficits in approximately half of SSc patients. These results are consistent with a previous study by Nobili, (2002).

The ageing process should not have influenced the SPECT results, since an age-matched control group was preselected for the statistical comparisons. In addition, there was no significant difference between SSc patients with a normal SPECT scan and those with hypoperfusion as regards age and disease duration.

The incidence of multiple white-matter hyperintensities with MRI was higher in patients with diffuse cerebral hypoperfusion. This result is consistent with the study of Cutolo et al. (2000).

MRA showed normal findings at the major vascular supply of the brain in those SSc patients who had positive MRI findings. The role of macrovascular involvement in SSc, which has been reported previously (Collidge & Blech 1995 and Veale et al., 1995), is consistent with MRA findings in only one patient where the anterior, middle and both posterior cerebral arteries were involved.

Accordingly, the SPECT abnormalities may be limited to the microangiopathic damage of brain vessels. It is believed that complex endothelial cell dysfunction leading to typical non-inflammatory microangiopathy. It is characterized by vascular tissue proliferation and obliterator microvascular lesions, which might alter the function of the nervous system during SSc (Herrick, 1995).
It is known that collagen types I, III & IV contained in the basement membranes of vessel walls, including the brain, are overproduced in SSc and are involved in the process of vascular narrowing and occlusion (Rutka et al., 1988). Nevertheless, the rarity of clinical CNS involvement in SSc has been attributed to the limited presence of extracellular matrix proteins (i.e. collagens) into the cerebral tissue with the consequent sparestness of media and adventitia in cerebral arteries and limited progression of the vascular obliteration (Averbuch-Heller et al., 1992).

Brain hypoperfusion as detected by SPECT has been reported in several rheumatic conditions, including chronic fatigue syndrome and systemic lupus erythematosus. Several combinations of rCBF defects both in the cortical regions and in the deep nuclei have been reported in different rheumatic diseases. A specific pattern of hypoperfusion could not be identified (Nossent et al., 1991 & Goldstein et al., 1993).

The increasing incidence of white-matter MRI abnormalities in SSc patients with diffuse hypoperfusion fits the hypothesis of cerebral microangiopathy. The findings of cortical hypoperfusion with SPECT in patients with deep white-matter lesions with MRI may be explained by assuming functional deafferentation of the cerebral cortex from the deep structures, through the ascending neural pathways such as thalamocortical projections, as observed in cerebral ischemia (Takano et al., 1985).

The severity of cerebral microvascular impairment during SSc might remain at a subclinical level but which can be revealed by appropriately sensitive techniques, such as high-resolution perfusional SPECT of the brain (Nobili et al., 1997).

**Conclusion:**

Focal or diffuse cerebral hypoperfusion has been found in a large number of neurologically asymptomatic SSc patients. Hypoperfusion seems to be unrelated to age or disease duration in SSc. SPECT was more sensitive than MRI in reflecting changes of cerebral blood flow in SSc.

**REFERENCES**


دالّة في نقص نثر الدم في المخ بواسطة جهاز الأشعة المقطعة لبث الفوتوتات أحادية المنشأ في مرضى التصلد الجهازي المصريين

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الأهداف: تهدف هذه الدراسة إلى تحليق تدفق الدم في المخ بواسطة جهاز الأشعة المقطعة لبث الفوتوتات أحادية المنشأ في حوالي أثني عشر مريض بالتصلد الجهازي مقابلة بجهاز جهاز التصلد الآلي. من الأحياء متقاربة في السن.

الطريقة: تم استبعاد مرضى ضغط الدم المرتفع ومرضى السكر والفشل الكلوي حيث هذه الأمراض قد تؤثر على نتائج الجهاز. وقد تم دراسة العلاقة بين نتائج جهاز الأشعة المقطعة لبث الفوتوتات أحادية المنشأ مع البيانات الإكلينيكية ونتائج الزمن المغناطيسي.

النتائج: نتج عن هذه الدراسة وجود ما يقرب من 54.5% من المرضى يعانون من نقص في نثر الدم في المخ حيث 66.7% نقص بوري وحوالي 33.3% نقص منتشر بواسطة جهاز الأشعة المقطعة لبث الفوتوتات أحادية المنشأ. كما أنه وجدت تغيرات بالزمن المغناطيسي في حوالي 33.3% من المرضى، كذلك نفى البحث وجود علاقة ذات دلالات إحصائية بين نتائج جهاز الأشعة المقطعة لبث الفوتوتات أحادية المنشأ وعمر المريض، وفترة المرض، ولفظ أعضاء أخرى متأثرة بالمرض.

الاستنتاج: نستنتج من هذه الدراسة وجود نقص بوري ومنتشر في وظيفة نثر الدم في المخ فيما يقرب من أكثر من نصف مرضى التصلد الجهازي بدون أي أعراض عصبية.