

THESIS OF UNIVERSITY DOCTORAL (Ph.D.) DISSERTATION

ISOTOPE DIAGNOSTIC EVALUATION OF CERTAIN ORGAN MANIFESTATIONS  
OF SYSTEMIC AUTOIMMUNE DISORDERS

DR. JÁNOS GAÁL

1ST DEPARTMENT OF INTERNAL MEDICINE, MEDICAL HEALTH CENTER,  
UNIVERSITY OF DEBRECEN  
DEPARTMENT OF RHEUMATOLOGY, KENÉZY GYULA HOSPITAL  
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## INTRODUCTION

Our knowledge about the pathogenesis and natural history of systemic autoimmune disorders is increasingly growing. The patient care of autoimmune disorders is a considerable challenge even for experienced clinicians. These disorders accompanied by various organ manifestations, and the early diagnosis of these manifestations may influence the quality of life and life expectancy of the patients. The routine laboratory methods serve only indirect information about the involvement of certain organs, while the major part of the imaging procedures can demonstrate only longstanding anatomical abnormalities. On the other hand, the great advantage of isotope diagnostic methods is the ability to follow and image the biochemical and physiological processes. These procedures can consider as applied physiological methods and can provide information about the function of certain organs. The possibilities implied in nuclear medicine in the field of clinical immunology are not utilised by far, and we have few data about the capability of scintigraphic methods.

In the present work I relate my experiences of examinations made in three topics:

1. The myocardial involvement of patients with progressive systemic sclerosis (PSS), using gallium-67-citrate (Ga-67-citrate) scintigraphy.
2. The abnormalities of esophageal motility in patients with mixed connective tissue disease (MCTD), by esophageal transit scintigraphy.
3. The ability of Tc99m HMPAO labelled leukocyte joint scintigraphy in the assessment of disease activity in patients with rheumatoid arthritis (RA).

## OBJECTIVE

I was looking for answering the question that how can assist the modern isotope diagnostic methods the detection of certain organ manifestations of systemic autoimmune disorders. I tried to clarify the usefulness of these methods on patient care and management and in the measurement of the effectiveness of the treatment.

1. It is presumable that – at least in party - myocardial inflammation takes part in myocardial involvement of PSS patients. Reliable diagnosis of this complication can be achieved by endomyocardial biopsy. There was no attempt with non-invasive methods in detection of myocardial involvement untill now. Ga-67-citrate scintigraphy, a method used for detection of septic foci, can be potentially suitable for this purpose. We performed myocardial Ga-67-citrate scintography in 16 PSS patients cared by III. Department of Internal Medicine Medical Health Center, University of Debrecen. We tried to answer the following questions:
  - Can be detected abnormal Ga-67-citrate myocardial uptake in PSS patients?
  - Is there any difference in frequency of increased myocardial Ga-67-citrate accumulation between the control (investigated from other causes) and PSS group?
  - Can be drawn any connection with the scintigraphic results and the clinical and laboratory parameters of the PSS patients?
  - Whether myocardial radiogallium scintigraphy is capable to image inflammation in progress in myocardial tissue?
  
2. The esophageal involvement is the most frequent gastrointestinal manifestation in patients suffering from MCTD. Detection of this complication was performed by traditional X-ray studies untill now. Clinical experiences show that X-ray studies cause significant discomfort and unnecessary radiological burden for the patients. Esophageal transit scintigraphy can be a potential alternative in the diagnosis of esophageal motility disorders. We performed radioisotope transit studies in 22

MCTD patients cared by III. Department of Internal Medicine Medical Health Center, University of Debrecen. We were looking for answering these questions:

- Can be detected the lengthening in the esophageal transit time in MCTD patients?
- How often can be find this abnormality in patients without any gastrointestinal complaint?
- Which agreement can be found between findings of scintigraphic and radiological transit studies?
- Can be demonstrated any statistically significant correlation between scintigraphic, radiological and clinical data?
- Is esophageal scintigraphy suitable in the early detection of esophageal involvement in MCTD patients?

3. Arthritis activity is the most powerful clinical variable that determines the therapeutic approach of patients with RA. There were several efforts for numeric expression of disease activity in RA, but the several variables (activity indices) don't fulfilled the expectations, presumably because of subjectivity of evaluation and the lacking specificity of laboratory findings. Imaging and quantifying of synovitis is a great challenge for nuclear medicine, and several efforts are in progress in this field. We investigated 21 RA patients cared by I. Department of Internal Medicine Medical Health Center, University of Debrecen using Tc99m HMPAO-labeled leukocyte joint scintigraphy. We tried to answer the following questions:

- Can Tc99m-HMPAO-labeled leukocyte joint scintigraphy demonstrate rheumatoid synovitis?
- How can be quantied the synovial inflammation?
- Which correlation can be detectable between the cumulative radiopharmakon uptake index, developed by us, and the degree of synovitis?

- Can be drawn any association between the Disease Activity Score (DAS) - an index validated by EULAR- and the cumulative radiopharmakon uptake index?
- Can be monitored the disease activity by scintigraphic examination?
- What is the exact role of Tc99m-HMPAO scintigraphy in the diagnosis of joint pain with unknown origin and early arthritis?

## LITERATURE OVERVIEW

### **1. The forms of cardiac involvement in PSS**

#### *1.1. Primary cardiac involvement*

The estimated prevalence of primary cardiac involvement is around 50% according to postmortem studies. The main forms are the pericarditis, cardiac failure developed in base of chronic myocardial fibrosis, myocarditis, rhythm disturbances, and cardiac valvular disease.

Necropsy studies found the frequency of pericardial involvement being between 33 and 70%. The acute and chronic fibrinous pericarditis, pericardial adhesions and exudative pericarditis belongs to this entity.

Cardiac failure, developed in base of chronic myocardial fibrosis occurs in less than 5%, most often in patients with diffuse cutan sclerosis. It seems that the underlying pathomechanisms are the intermittent longstanding vasospasm in connection with Raynaud phenomenon and chronic ischemia. These hypothesis is supplied by autopsy data showing widespread degeneration and substitutive fibrosis of myocardial fibers and so called "contraction band necrosis". The last one is drown in connection with "intramyocardial Raynaud phenomenon". Some investigators found concentric intimal hypertrophy, narrowing, fibrosis and fibrinoid necrosis of intramural coronary arteries and arterioles. Primary myocardial fibrosis was showed by Hungarian authors, supplied by echocardiographic examinations as well.

The myocarditis with the "classic" ECG, echocardiographic findings and the elevated creatinine kinase MB or LDH isoenzyme levels is a rare finding in patients with systemic sclerosis (SSc) and hard to diagnose, because endomyocardial biopsy is rarely performed in our country and the proportion of the false negativity is relatively high. It can be assumed that the inflammation component takes part in several different forms of the cardiac involvement. Autopsy studies demonstrated myocarditis in up to 30% of patients by histology, some authors suppose connection between the myocarditis and skeletal myositis. The inflammation progressing in the myocardial tissue can be asymptomatic.

Various forms of rhythm abnormalities can be found, like supraventricular tachyarrhythmias (atrial fibrillation, flutter, supraventricular extrasystolia, sinus tachycardia), ventricular ectopias (ventricular extrasystolia, ventricular tachycardia), but conduction disturbances progressing to AV block are not rare findings in SSc as well. A peculiar conduction abnormality is reported in SSc, mimicking septal myocardial infarction. The disturbance of autonomic innervation of the heart is shown in PSS using 24 hour heart rate variability analysis.

Valvular abnormalities are uncommon in SSc, and if they occur, mostly are in connection with the antiphospholipid syndrome.

### *1.2. Secondary cardiac involvement*

Consequences of pulmonary hypertension affecting mainly the right heart chamber are not uncommon findings in the limited and diffuse scleroderma subgroup as well. The systemic hypertension associated with renal involvement often causes left heart failure and occurs rather in patients with diffuse scleroderma.

## **2. The disturbances of esophageal motility in patients with MCTD**

The significant proportion of connective tissue disorders is characterized by the esophageal involvement, but this causes symptoms in only a part of patients, and even severe hypomotility can occur without dysphagia. Esophageal motility disorders are common in PSS, but in MCTD there are few controlled studies. The main clinical forms are the upper esophageal dysfunction, diffuse aperistalsis, lower sphincter involvement. The decreased pressure and dysfunction of upper esophageal sphincter is quite frequent, some investigators observed the cessation of functional abnormalities of upper esophageal sphincter after corticosteroid treatment.

The diffuse hypoperistalsis or aperistalsis, affecting the whole esophageal body can be detected by manometry in up to half of the MCTD patients. Certain studies showed correlation between the esophageal dysmotility and the presence of Raynaud phenomenon, others observed that peristalsis tends to be normal after corticosteroid treatment.

17% of the MCTD patients had distal aperistalsis and 43% had lower amplitude of peristaltic pressures in the distal esophagus using manometry. Several studies found lower

esophageal sphincter pressure in the distal esophagus comparing to the normal controls. The systemic corticosteroid treatment given because of other major organ involvement improved the lower esophageal sphincter pressure significantly.

### **3. The significance and measurement of disease activity in RA patients**

The most important factor affecting the therapeutic strategy in RA is disease activity, which should be determined in every single visit to follow the course of disease and the effectiveness of the therapy.

Several authors developed articular indices, the most widely known are the Ritchie index examining 53 joints and the Thompson-Kirvan index examining 38 joints. According to present knowledge there is no clinical parameter or laboratory finding which can reflect disease activity solely. Disease activity should be represented by a set of variables which can be reported and analysed either separately or as part of an index of the disease activity. In the past, numerous measures have been used as endpoint measures of disease activity in clinical trials. Recommendations about what instruments to use for each item were made by the European League Against Rheumatism (EULAR) and by the American College of Rheumatology (ACR). The demand for numeric expression of disease activity has been a great challenge for a long time, several activity indices were developed in the past. The most widely used and most relevant is the Disease Activity Score (DAS), described firstly by Van der Heijde in 1990. Several versions of DAS were described and evaluated since then, the most wide-spread is the 4 variable DAS 44, validated by EULAR in 1996. It can be calculated as following:  $DAS = 0,54 \times \sqrt{RAI} + 0.065 \times Swjts + 0.33 \ln ESR + 0.0072 \times GH$

where RAI= Ritchie articular index, Swjts = the number of swollen joints, ESR = erythrocyte sedimentation rate, GH = general health status quantified on a 100 mm visual analogue scale.

Not only disease activity, but therapeutic response can also be judged by the difference between the baseline and subsequent DAS score as well.

## PATIENTS AND METHODS

### **1. Myocardial Ga-67-citrate scintigraphy of patients with PSS**

#### 1.1. Patients

Sixteen patients with SSc were investigated. Cases during hospital admission were randomly selected for the study. All patients fulfilled the diagnostic criteria for systemic sclerosis. The clinical and laboratory data of patients were evaluated by a standard protocol. Twelve of these cases had some cardiac symptoms in their case histories. Five cases showed a pericardial thickening indicating an earlier pericarditis. Nine patients had retrosternal chest pain characteristic of angina pectoris in their case histories. Signs of ischemia were detected on the resting ECG in two of these patients and during the stress test by bicycle ergometer in another case. Of the 6 remaining cases, three did not show any ECG abnormalities during exercise, while the investigation was not performed for the other three cases because of muscle weakness and/or polyarthritis.

#### 1.2. Gallium-67 imaging of the heart

Gallium-67 imaging was performed 72 hrs after the intravenous administration of 200 MBq Ga67-citrate (ATOMKI, Debrecen, Hungary). Images were taken using a large-field-of-view gamma camera (MB-9200, Gamma Művek, Hungary), equipped with a medium energy, parallel-hole collimator. For the first patient single-channel acquisition was used ( $185 \text{ keV} \pm 20\%$ ), and images were acquired until either 15 min or 400000 counts had been reached; later it was changed for two-channel acquisition ( $185 \text{ keV} \pm 20\%$  and  $93 \text{ keV} \pm 15\%$ ), resulting in much higher count rates, and thus allowing for better statistics and shorter acquisition time (12 min or 1 million counts). 128x128 images were stored and evaluated using a dedicated computer system (DIAG). Both raw and Metz-filtered images were displayed, and the intensity of gallium uptake in the projection of the heart was compared to that of the sternum.

The evaluation of the isotope uptake of the myocardium was performed blindly without any information about the clinical-laboratory findings of the particular patient. The images were graded on a scale of 1 to 4. 1=no definable or barely perceptible activity over the

myocardium; 2=definite myocardial visualization but decisively less intensive than in the sternal area; 3=myocardial activity almost equal to that of sternum; and 4=myocardial intensity greater than that of the sternum. Patients who had gallium-67 uptake of grade 2 were considered as weakly positive, while those who had grade 3 or 4 were considered as unequivocally positive.

Eighteen age matched patients without any evidence of cardiac disease were also evaluated as controls. The clinical diagnoses of these cases were osteomyelitis, sarcoidosis, gluteal abscess, femoral head necrosis, chronic cholecystitis, splenic abscess, caecum tumor, Burkitt's lymphoma, and periappendicular abscess, each in one case. Furthermore, four patients with fever of unknown origin, and five cases with Hodgkin's disease were also investigated as controls. All the control cases showed an insignificant or no uptake (grade 1), apart from one control case exhibiting a grade 2 gallium-67 uptake.

### 1.3. Echocardiographic studies

All cases were simultaneously investigated by echocardiography as previously described. Cases exhibiting signs of pericarditis were excluded from the study.

#### 1.4. Magnetic resonance imaging (MRI)

Cases with a positive gallium uptake were also investigated by MRI to rule out the presence of the enlargement of mediastinal lymphonodes and pericarditis (Shimadzu SMT 100X, Japan) (1 TESLA). The examinations were performed in supine position, using body coil. We used cardiac gating to accommodate for motion, and pulsation artifacts. The scans were performed with 10 mm slice thickness and the section gap was 10 mm as well. Axial and coronal scans were performed from the thoracic outlet to the diaphragmatic region, by T<sub>1</sub> and T<sub>2</sub> weighted imaging. No contrast material was used. Less than 21 days elapsed between the gallium imaging and the MRI.

## **2. Tc99m DTPA esophageal transit scintigraphy in patients with MCTD**

### 2.1. Patients

22 MCTD patients cared by 3rd Department of Internal Medicine, Medical Health Center, University of Debrecen were investigated. All patients fulfilled the diagnostic criteria of MCTD worked out by Alarcon-Segovia and Villareal in 1987. The average age at establishing the diagnosis was 39.8±8.8 years, the average follow up time was 9.8±3.2 years. The frequency of clinical symptoms were: arthralgia in 82%, arthritis in 23%, Raynaud phenomenon in 77%, swollen hands in 68%, myositis in 59%, skin alterations in 32%, vasculitis in 8%, dysphagia in 59%, esophageal motility disturbances observed in X-ray studies in 54% were detectable. In addition anti-SSA and anti-cardiolipin positivity in 41-41%, anti-SSB positivity in 4.5 %, increase in serum polyclonal immunoglobulin in 59% were observed.

### 2.2. Examination of esophageal motility by Tc99m DTPA scintigraphy

The patients were examined in lying position after an overnight fasting. After a test swallow the patients swallowed 20 Mbq DTPA dissolved in 10 tap water. Afterwards they were asked not to swallow for 60s, and then to make a “dry” swallow and repeat it after 30 s. The intraesophageal transport of the radiopharmaceutical was followed and imaged by a gamma camera (MB-92000, Gamma Müvek), 128x128 images were stored and evaluated using a dedicated computer system (DIAG).

During the data collection after the first swallow the digital images were made with higher (1s/frame) frequency, and then with lower (2s/frame) frequency. During the data processing the ROI-s (Region Of Interest) were assigned, time-activity curves and parametric pictures were made from the whole esophageal body and from the upper, the middle and the lower third, and from that part of stomach which gets in visual field. The quantitative assessment of passage were made using time-activity curves. The transit time was determined, which is by definition the time elapsed between the appearance of the radiopharmaceutical to the emptying of the 90%-of the peak activity. The qualitative assessment lies on the shape of the time-activity curves and on the parametric (condensed) pictures, the parametric images are used for the diagnosis of retrograde motion as well.

Despite the small number of cases the correlation between the scintigraphic data and clinical parameters of activity were analyzed statistically using Student's t-test.

### **3. Tc99m HMPAO labelled leukocyte joint scintigraphy of the patients with RA**

#### 3.1. Patients

Twenty-one patients cared by 1rd Department of Internal Medicine, Medical Health Center, University of Debrecen with definitive RA according to the American Rheumatism Association criteria were studied. There were eighteen women and three men. The mean age at the time of establishing the diagnosis was  $52.2 \pm 15.5$  years, the disease duration ranged from 0.25 years to 29 years with a mean duration of  $8.35 \pm 8.54$  years. The rate of seropositivity was 62%, rheumatoid nodule was present in 24%, and ANF positivity was found in 14% of patients. Radiographs of hands and feet showed joint erosions in 76% of patients. Ten patients were treated with corticosteroids at the time of the study. Informed consent was obtained from all patients and the protocol was approved by the Ethical Committee of the University of Debrecen, Medical Health Center.

#### 3.2. Methods

The clinical and laboratory parameters were collected and fully analyzed. The Disease Activity Score (DAS) - proposed and validated by EULAR - was calculated in every case by the following formula:  $DAS = 0.54\sqrt{RAI} + 0.0065 (SwJts) + 0.33 (\ln ESR) + 0.0072$

(GH), where RAI = Richie articular index, SwJts = the number of swollen joints, ESR = erythrocyte sedimentation rate, GH= general health status by 100 mm visual analogue scale.

50 ml of heparinised whole blood was withdrawn from each patient. Leukocytes of the patients were separated and labeled with 500-700 MBq Tc-99m using LEUCOSCINT kit (FJCSSKI, Hungary), according to the instructions of the manufacturer. The labeling efficiency was above 80% in all cases. The Tc-99m labeled leukocytes were reinjected into the patients intravenously. The injected radioactivity was measured with a dose calibrator, and converted to counts/sec using the calibration factor measured for the camera-collimator system previously. Static images of the wrists, hands, elbows, shoulders, hips, knees, ankles and feet were acquired 4 h after the administration of the labeled leukocytes. The images were acquired into 128\*128 matrices, until either 600 000 counts or 8 min were reached, using MB-9200 gamma camera (Gamma Move, Hungary) equipped with LEOP collimator. The images were (a) evaluated visually in a semi-quantitative manner; and (b) the regional uptakes of the radiopharmaceutical were calculated for the feet and hands. Regions of interest (ROI-s) were drawn around the wrists, hands, ankles and feet, and their uptake was expressed as a percentage of the injected dose (corrected for Tc decay). The regional radiopharmaceutical uptakes of the mentioned joints were summed up to form a single uptake parameter.

Ten age matched patients, investigated because of other disease and without any joint complaint, were also evaluated as controls. The clinical diagnoses of these cases were breast cancer, chronic cholecystitis, and gluteal abscess in one case. Furthermore, four patients with fever of unknown origin and three cases with osteomyelitis were also investigated as controls. All the control cases showed no significant radiopharmaceutical joint uptake.

The correlation between the scintigraphic data and clinical parameters of activity were analyzed statistically using linear regression analysis, variance analysis, and Student's t-test.

## RESULTS

### **1. Myocardial Ga-67-citrate scintigraphy of patients with PSS**

Five patients with SSc showed an increased cardiac gallium-67 uptake. In four cases, the scans were interpreted as unequivocally positive (the intensity was nearly equal to that of the sternum), the remaining case exhibited a weakly positive Ga-67 scan (grade 2).

Three of the positive cases belonged to the diffuse scleroderma subset. No difference was found between the mean follow-ups of the positive and negative cases. Patients showing an increased gallium-67 uptake were considerably older compared to the rest of the patients ( $60,8 \pm 5,0$  versus  $44,6 \pm 10,7$  years, respectively;  $p < 0,007$  by t-test), but no difference was found between the two groups in the mean disease duration. The onset of disease in patients showing a positive Ga-67 scan was  $54,6 \pm 9,5$  versus  $35,3 \pm 10,4$  years in the negative cases. The mean skin scores for the positive and negative groups were similar. None of the positive cases had myositis.

No elevated enzyme levels of creatine kinase MB, lactate dehydrogenase isoenzyme, and/or clinical, ECG findings characteristic of myocarditis were ever detected in these positive cases. No signs of pericarditis were detected by echocardiography. Furthermore, the systolic and diastolic function parameters including the end diastolic and end systolic volume, ejection fraction, fractional shortening, E/A ratio, and isometric relaxation time were not different in cases with positive gallium scintigraphy versus the rest of the other patients (data not shown).

Magnetic resonance imaging was also performed in the five positive cases and showed no signs of enlarged mediastinal lymphonodes or pericarditis as potential causes of the positivity in the isotope uptake.

### **2. Tc99m DTPA esophageal transit scintigraphy in patients with MCTD**

During the follow up of the oesophageal transit of radiopharmaceutical the lengthening of the transit time was observed in 59% of the patients. This tendency was perceivable in 54% of patients using traditional X-ray study. Among patients with dysphagia both methods detected positivity in 8-8 cases. The scintigraphic and radiographic results were compared and found that there is no significant correlation between them using Fisher-extraction test

(presumably because of low number of cases). Those patients with lengthened transit time in scintigraphic studies were characterised by higher age at diagnosis ( $41.3 \pm 11.9$  years) than patients with normal esophageal transit ( $38.5 \pm 9.8$  years). There were no significant correlation between the scintigraphic data and other clinical or laboratory parameters, presumably due to low case number.

### **3. Tc99m HMPAO labelled leukocyte joint scintigraphy of the patients with RA**

A relatively high average DAS score ( $4.72 \pm 1.07$ ) was found in the patients. The regional radiopharmaceutical uptake was increased only in the small joints of the hands and feet in the great majority of patients, therefore this parameter was calculated for these regions. The degree of accumulation of Tc-99m HMPAO labeled leukocytes showed no correlation with the patients' age, gender, duration of disease, visual analogue scale (VAS), Richie index, DAS or any laboratory parameters. Significant correlation  $p < 0.01$  was found, on the other hand, between the regional radiopharmaceutical accumulation in the hands and feet, and the swollen joint count.

## **DISCUSSION, PRACTICAL IMPORTANCE OF RESULTS**

### **1. Myocardial Ga-67-citrate scintigraphy of patients with PSS**

The myocarditis with "classic" ECG, echocardiographic findings and the elevated creatinine kinase MB or LDH isoenzyme levels is a rare finding in patients with SSc. The prevalence of myocardial fibrosis can reach 81%, and this high proportion of cases with fibrosis may not be fully explained by the secondary consequences of myocardial ischemia caused by episodic vasospasm and/or vascular abnormalities of the heart in SSc.

The initiating events in SSc are characterized by inflammatory signs involving T lymphocytes and monocytes/macrophages in both the skin and lung involvements of the disease. It is tempting to speculate that the early myocardial involvement is also accompanied by inflammatory signs.

A simple and reliable method for the detection of a silent myocardial inflammation is still lacking. Endomyocardial biopsy is highly specific, but its sensitivity is questionable

because the inflammation may be focal or patchy. The need for a special center with trained personnel and the potential risks involved in the investigation are further disadvantages of this method. Myocardial gallium-67 citrate scintigraphy as a noninvasive simple method for the possible detection of cardiac inflammation may have a considerable value in the diagnosis of myocarditis.

In our five positive cases, the increased gallium uptake may be due to a chronic interstitial inflammation of the myocardium. The speculation that the increased cardiac radiogallium uptake is a possible indicator of myocardial involvement still needs to be confirmed by endomyocardial biopsy.

Although the number of cases is low, it is also tempting to speculate that elderly patients with a disease onset around 60 years tend to be the candidates for the positive gallium-67 scintigraphy. One of the contributing factors leading to the poor prognosis of the elderly cases with SSc may be the silent myocardial interstitial inflammation which can be present in both the diffuse and the limited scleroderma subsets.

The closer follow, observation and cardiac monitoring of those patients with positive myocardial gallium-67-citrate scintigraphy may contribute to improving survival and earlier perception of cardiac complications.

## **2. Tc99m DTPA esophageal transit scintigraphy in patients with MCTD**

The most often used methods in examination of esophageal motility disorders are the radiographic esophageal passage, gastroscopy, 24-hours manometry and pH-monitoring. The radiographic passage studies using gastrografin or barium could depict anatomical alterations, but its sensitivity in demonstration of subtle motility abnormalities is low, interpretation is subjective and has significant radiation burden. Esophagoscopy can show correct anatomical picture from gastric mucosa and anatomy, but its value in motility disorders is limited. The 24-hours manometry and pH-monitoring are highly sensitive, but are not acceptable for most of patients because of its invasivity.

Significant proportion of connective tissue disorders characterised by esophageal involvement, this is particularly true for fibrosing diseases. The dysfunction can precede the organic alterations. The reliable diagnosis of esophageal motility disorders is important for gastroenterologist and rheumatologist as well. The esophageal involvement is the most

frequent gastrointestinal manifestation in MCTD patients, which not threatens the life directly, but may contribute considerably to the worsening of quality of life.

The esophageal involvement can occur in the absence of esophageal symptoms, therefore it's early detection and treatment has great importance. The dysfunction of upper sphincter is particularly meaningful because this can lead to repeating aspirations. Several studies refer to a myositis in the background of functional abnormalities, especially in early cases. This dysfunction can be relived using systemic corticosteroid treatment in proper timing. Our results show that scintigraphic examination detected prolonged esophageal transit time in high percent of cases. Obviously, these data require confirmation in a larger patient pupulation, we intend to repeat scintigraphic examination and to combine with esophagoscopy and manometry. In patients with MCTD we recommend to perform esophageal scintigraphy even if the absence of esophageal symptoms to screen the occult esophageal involvement. Though literature data are inconsistent, it is temping to speculate, that esophageal dysfunction can be influenced favourably with early corticosteroid or immunosuppressive treatment. Our method is a modified version of esophageal radionuclide transit scintigraphy suggested by other investigators, which is well tolerated by the patients because of minimal time requirement and the quickness of computer data processing. The radionuclide transit scintigraphy is a safe, generally available with easy performance, quick, inexpensive method, which can be accomplished every nuclear medicine laboratory supplied with a gamma camera. It's additional advantage is that it can be performed with a swallowing physiologic material, is reproducible, quantifiable, convenient for the patient and it's radiation burden is very low. Last, but not least it can be repeated without restraint and (regarding that it is strictly quantitative due the computer data processing) the individual examinations performed in different point of time can be compared, and the effectivity of treatment can be measured in this manner. According to literature data the sensitivity in diagnosis of secunder motility disorders is between 44%-92% depending on patient population, but in certain disorders (for example in achalasia) it can achieve even 100%, the specificity varies between 71% and 88%. There are just few clinical experience in patients with MCTD, but the use of esophageal scintigraphy in clinical assessment ant follow up is suggested by all means, because just early esophageal involvement can be influenced by corticosteroid or immunosuppressive treatment.

### **3. Tc99m HMPAO labelled leukocyte joint scintigraphy of the patients with RA**

The availability of an objective and reproducible method to evaluate arthritis activity in RA would be of great value in patient management and in the assessment of the therapeutic effect. The evaluation of inflammation in arthritic joints is a matter of subjective judgement, and hence has poor reproducibility. It is known that the ESR is a non-specific finding, and that patient's pain tolerance and judgement of general health are quite different. The possibility of a direct visualization of the arthritic joint is the great advantage of scintigraphic techniques compared with other modalities, and the radiopharmaceuticals may image joints which are difficult to assess clinically or by means of radiography. Furthermore, they may hypothetically detect joint inflammation in an early phase. In Europe, DAS is the most widely used activity index of rheumatoid arthritis. It combines the Ritchie articular index, a count of swollen joints, the erythrocyte sedimentation rate (ESR), and an assessment of the patient's general health. According to clinical observations rheumatoid synovial fluid has a high neutrophil content in active phases of the disease, accordingly increased neutrophil accumulation due to neutrophil chemotaxis may indicate an active synovitis. Up to now, procedures for imaging joint inflammation were radiological, with substantial irradiation burden. They provide only indirect information about synovitis and are able to detect only definitive erosions (conventional X-ray, CT), or are rather costly and have a long waiting time. MRI of the wrist has been shown to be more sensitive for the detection of early erosions than plain radiography in a recently published study, and may thus herald joint damage. After all, in management decisions its use is not widely accepted and its applicability in assessment of disease activity for the time being is still pending. The capability of scintigraphic methods for imaging synovial inflammation has not been extensively tested so far. There were attempts with Tc99m pertechnetate, Tc-99m diphosphonates, Ga-67 citrate, In-111 chloride, Tc99m labeled liposomes, Tc-99m nanocolloid, lymphocytes, J001, In111 or Tc99m labeled human non-specific immunoglobulins, labeled antibodies against CD3, CD4, E-selectin, TNF $\alpha$ , IL1, IL2, IL6 and somatostatin. Most of them are too expensive for routine use, and the function of labeled lymphocytes are unstable. Promising results have been obtained with the use of In111 or Tc99m labeled human non-specific immunoglobulins with relatively high sensitivity for imaging synovitis. The disadvantage of this method is

the low specificity (25-50%) and relatively high cost compared to leukocyte scintigraphy. In addition the mechanism of non-specific IgG accumulation at site of inflammation is still unclear. Increased vascular permeability, specific trapping of IgG by Fc receptors located on inflammatory cells, have been suggested. The method proposed in this paper is the Tc-99m labeled leukocyte scintigraphy because of its low cost and radiation load, general achievement, and relatively simple preparation method. It appears that Tc99m HMPAO labeled leukocyte joint scintigraphy has clinical usefulness in quantitative assessment of neutrophil migration into inflamed joints and the rheumatoid arthritis activity. Our results show a significant correlation between the local manifestation of the active disease (swollen joint count) and radiolabeled leukocyte accumulation. Further investigations are necessary in an extensive patient population to elucidate the role of labeled leukocyte scintigraphy in the evaluation of rheumatoid arthritis activity.

## CONCLUSIONS

### **1. Myocardial Ga-67-citrate scintigraphy of patients with PSS**

We showed, that:

1. There is an increased myocardial Ga-67-citrate uptake during Ga-67-citrate scintigraphy in a part of patients.
2. The patients with positive scintigraphy tended to be older and the age at time of diagnosis was higher.
3. The scintigraphic screening of patients, characterised by advanced age and later disease onset can be suitable for the early demonstration of myocardial involvement and for the prediction of less favourable prognosis.

Silent myocardial involvement can be suspected in a significant proportion of PSS patients. The increased myocardial radiopharmaceutical uptake during radiogallium scintigraphy refers to inflammatory myocardial involvement in all probability and accounts for closer observation. We included a new method in the investigation protocol of PSS patients.

### **2. Tc99m DTPA esophageal transit scintigraphy in patients with MCTD**

We showed, that:

1. In a significant proportion of MCTD patients esophageal involvement can be detected.
2. The motility abnormalities can occur in a part of MCTD patients free from esophageal complaints.
3. The scintigraphic results do not shown unequivocally correlation with the results of conventional X-ray studies.
4. In the patient population characterised by lengthened transit time, the average age at time of diagnosis was more advanced than in patients with normal esophageal transit.
5. The radionuclide esophageal scintigraphy can be suitable for detecting of early esophageal involvement especially in asymptomatic patients.

The regular screening of MCTD patients with later disease onset is particularly suggested. We inserted a simple, non invasive but highly sensitive and specific new diagnostic method into the investigation protocol of MCTD patients, which capable of detecting the most frequent gastrointestinal complication of this disease.

### **3. Tc99m HMPAO labelled leukocyte joint scintigraphy of the patients with RA**

We showed, that:

1. Synovial inflammation of RA patients can be detected by Tc99m HMPAO labelled joint scintigraphy.
2. The extent of synovitis can be quantify for each joint region, forming a scintigraphic index.
3. Summing these indices a global radiopharmaceutical uptake index can be form.
4. This cumulative radiopharmaceutical uptake index shows statistically significant correlation with the local manifestation of the active disease (swollen joint count).
5. The scintigraphic examination can be applied for monitoring of the disease activity in RA.

The participation of inflammatory component in the etiology of joint pain with unclarified origin can be demonstrate using Tc99m HMPAO joint scintigraphy, thus the inactive (“burned out”) RA can be separate from active synovitis. We inserted a safe, non invasive, but extremely specific scintigraphic method in the evaluation protocol of patients with RA, which can give assistance in everyday therapeutic decisions.

## PUBLICATION LIST

### The articles used in the dissertation

1. **Gaál J**, Hegedűs K, Czirják L. Myocardial gallium-67 citrate scintigraphy in patients with systemic sclerosis. *Ann Rheum Dis* 1995; 54: 856-858. **IF: 2,121**
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