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Clinical study *Klinikai tanulmány*

Predictive value of esophageal involvement in patients with undifferentiated connective tissue disease using radionuclide esophageal transit scintigraphy

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Objective: 1) To look for the frequency of esophageal dysfunction using radionuclide esophageal transit scintigraphy (RETS) in 145 patients with undifferentiated connective tissue disease (UCTD). 2) To seek the correlation between the clinical/laboratory data and scintigraphic alterations. 3) To determine clinical and laboratory indicators with predictive value for evolution to established connective tissue disease (CTD) in combination with scintigraphic results.
Method: 145 patients with UCTD were examined by Tc99m DTPA esophageal transit scintigraphy. The intraesophageal transport of the radiopharmaceutical was followed and imaged by a gamma camera, a series of 128x128 images were stored and evaluated. The correlation between the scintigraphic data and clinical and laboratory parameters was analyzed statistically.
Results: Unequivocally positive scintigraphy, indicative of motor abnormality was found in 45.5% of patients (n=66), 71.2% (n=47) of whom were without clinical symptoms. Significant correlation was found between the presence and severity of scintigraphic alterations and ANA, the anti-cardiolipin and anti β2 GPI autoantibody positivity, as well as the presence of skin rash. Scintigraphic positivity was significantly more frequent in patients evolving to definitive CTD (p=0.0178), and abnormal scan predisposed to transition into the definitive CTD (odds ratio: 2.292; CI: 1.61-4.525). Its cumulative positive predictive value was found to be 42.8% and cumulative negative predictive value 73.3% with regard to the development of a definitive CTD.
Summary: Author's results show that scintigraphic alterations together with clinical and laboratory alterations can help the clinician in the prediction of final outcome.

KEY-WORDS: UCTD, Esophageal involvement, Prognostic factors, Esophageal scintigraphy, Predictive value

A NYELŐCSŐ ÉRINTETTSÉG PREDIKTÍV ÉRTÉKE RADIONUCLID OESOPHAGEALIS TRANZIT SZCINTGRÁFIÁVAL VIZSGÁLT DIFFERENCIÁLATLAN KÖTŐSZÖVETI BETEGSÉGBEN SZENVEDŐ BETEGEKBEN

Célkitűzés: 1. Radionuclid oesophagealis szcintigráfiával (RETS) az oesophagealis diszfunkció kimutatása 145 differenciálatlan kötőszöveti betegségben (UCTD) szenvedő betegben. 2. Összefüggés keresése a klinikai/laboratóriumi adatok és a szcintigráfiás eltérések között. 3. A kötőszöveti betegség (CTD) kialakulásában és diagnosztizálásában prediktív értékű klinikai és laboratóriumi indikátorok meghatározása a szcintigráfiás eredményekkel kombináltan.
Módszer: Szerzők 145 UTCD-s beteget vizsgáltak Tc99m DTPA oesophagealis tranzit szcintigráfiával. A radiofarmakon intraoesophagealis transzportját gamma kamera követte, 128x128 képsorozatot tároltak és értékeltek. Statisztikailag elemezték a szcintigráfiás adatok valamint a klinikai és laboratóriumi paraméterek közötti összefüggést.
Eredmények: Motoros abnormitásra jellemző egyértelműen pozitív szcintigráfiás leletet találtak a betegek 45,5%-ában (n=66), akiknek 71,2%-a (n=47) teljesen aszimptomatikus volt. Szignifikáns korreláció volt kimutatható a szcintigráfiás eltérések jelenléte és súlyossága valamint az ANA, az anti-cardiolipin és anti β2 GPI autoantitest pozitivitás és a bőrkiütés között. Definitiv CTD irányába haladó betegeknél a pozitív szcintigráfia szignifikánsan gyakoribb volt (p=0,0178) és a szcintigráfiás eltérések prediszponáltak a definitiv CTD irányába való átmenetre (arányok: 2,292; CI: 1,61-4,525). A kumulatív pozitív prediktív érték 42,8%, míg a kumulatív negatív prediktív érték 73,3% volt a definitív CTD kialakulásának irányában.
Összefoglalás: Eredményeik szerint a szcintigráfiás eltérések a klinikai és laboratóriumi eltérésekkel együtt segíthetik a klinikust a végső kimenetel predikciójában.

KULCSSZAVAK: UCTD, Nyelőcső érintettség, Prognosztikus faktorok, Oesophagealis szcintigráfia, Prediktív érték

Introduction:

The established connective tissue diseases (CTDs) have universally accepted diagnostic criteria. In contrast to these CTDs, are a number of patients with symptoms and signs characteristic of CTDs, who do not fulfill the criteria for definitive CTDs. Esophageal involvement has been reported with most of the systemic connective tissue disorders [1], but only a subgroup of these patients have clinical symptoms, and even severe hypomotility can occur without dysphagia [2, 3]. Esophageal motility disorders are common in progressive systemic sclerosis (PSS) [4, 5], but fewer studies of esophageal involvement in other connective tissue diseases have been done. The scintigraphic evaluation of esophageal motility disorders is highly sensitive, and offers the most accurate assessment of the actual progression of a bolus of solid food or liquid through the oesophagus [6, 7]. A high correlation has been shown between esophageal scintigraphy and manometry, which is generally considered the gold standard for diagnosing motor dysfunction [8]. Some studies showed a correlation between esophageal dysmotility and the presence of Raynaud phenomenon, while others observed that peristalsis tends to be normal after corticosteroid treatment [3, 9, 10]. Till now, there has not been any such clinical study in patients with undifferentiated connective tissue disease (UCTD) in spite of the suspicion of high prevalence of esophageal involvement.

The objectives of this study were: 1. to determine the frequency of esophageal involvement in patients with UCTD 2. to investigate the correlation between the clinical/laboratory data and scintigraphic alterations and 3. to look for clinical and laboratory indicators with high predictive value for evolution to established connective tissue disease (CTD) in combination with scintigraphic results after an average two years of follow up.

Patients and methods:

Study population

The study population consisted of patients with UCTD under the continuing care of the specialized follow-up clinics of the 3rd Department of Internal Medicine, University Medical School of Debrecen. The diagnosis of UCTD was established according to the criteria described by *Wiliams et al.* in 1999 [11]. The diagnosis should be made in the presence of at least 3 of 11 specific clinical and laboratory markers of CTDs. These symptoms included Raynaud phenomenon, myalgia/myositis, arthritis/arthralgia, serositis, keratoconjunctivitis sicca, central nervous involvement, pulmonary symptoms, peripheral neuropathy, elevated erythrocyte sedimentation rate, rash and false positive serologic test for syphilis. Clinical and laboratory data (including screening for specific autoantibodies) were collected, recorded on a special data sheet, and fully analyzed. Antinuclear antibodies were determined by indirect immunfluorescence on rat liver sections and on Hep2 cell lines. ANA positivity was determined on liver sections and Hep2 cells on the basis of titers above 1:64 and 1:80, respectively. Specific autoantibodies, including anti-DNA, anti-Sm, anti-RNP, anti-ENA, anti-SSA, anti-SSB, anti Jo-1 and anti Scl70 were determined by ELISA (Cogent Diagnostics, UK).

During the 2 years after the scintigraphic examination the patients were closely monitored for the development of a definitive CTD. 145 patients were studied: 128 women and 17 men, with an age range of 18-74 years. The mean age at the diagnosis of UCTD was 41 (SD 12.6) years. The mean duration of symptoms at the time of entry into the study was 3.41 (SD 3.18) years. Thirty six patients were treated with corticosteroids (CS). Corticosteroid was administered when the patients had pericardial or pleural fluid, severe synovitis, CNS involvement or symptoms characteristic for systemic vasculitis. Daily dose varied between 4-12 mg/day, and the maximum duration was 6 months. 12 patients were treated with disease modifying agents at the time of the study. Informed consent was obtained from all patients and the Ethical Committee of the University of Debrecen, Medical and Health Science Centre approved the protocol.

Methods

Data acquisition: The patients were examined in the supine position after an overnight fasting. A Tc-99m-pertechnetate point source was used to mark the cricoid cartilage. After a test swallow the patients swallowed 20 MBq Tc99m-diethylene triamine pentaacetate (DTPA), dissolved in 10 ml of tap water. Afterwards they were asked not to swallow for 60 s, and then to make a „dry" swallow, repeated after 30 s. A series of 128x128 images were recorded by a gamma camera (MB-9200, Gamma Művek) interfaced to a dedicated computer system (DIAG), following the intraesophaegeal transport of the radiopharmaceutical. The image duration was 0.25 s during the first swallow (the first minute), and then 2 s during the second minute.

Data processing: Regions of Interest (ROI-s) were drawn around the whole esophageal body, as well as the upper, middle and the lower thirds of the esophagus, and that part of the stomach which appeared in the field of view. Time-activity curves were generated from all these ROI-s, and condensed images were also created as described below (see Figure 3-4.).

The rate of transit was characterized by the transit time calculated from each esophageal time-activity curve as the time elapsed from the appearance of the radiopharmaceutical until when the activity fell below 10% of the peak activity.

As the esophagus is a tubelike structure, the useful information of each image is limited to the line of the esophagus, and can be copied into a single column of a special condensed image. Thus a parametric image can be created, arranged so that the spatial distribution of the radioactivity along the esophagus is shown on the y axis, while time is represented by the x axis.

The pictures were analyzed both semiquantitatively (visual analysis), and quantitatively. For qualitative evaluation the shapes of the time-activity curves and the stripes of activity in the parametric images were assessed. The parametric images were used for the diagnosis of retrograde motion as well. The severity of alterations was graded on a scale of 0 (normal) to 3 where 1=the transit time is prolonged, but the 90% of peak activity leaved the esophagus; 2= less then 90% percent left the esophagus during the study; 3= there was observed only minimal emptying from the esophagus.

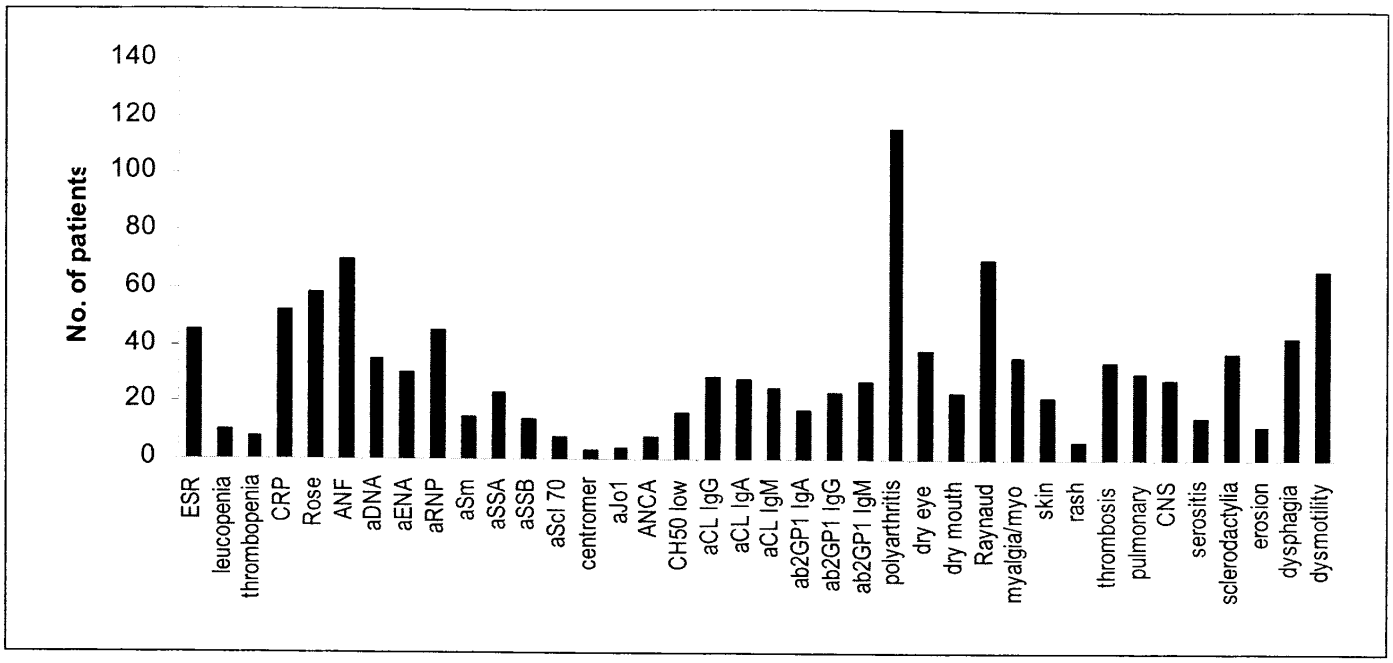

Figure 1. Clinical and laboratory data of 145 patients with UCTD

Statistical analysis: For the analysis of the correlation between the scintigraphic data and clinical or laboratory parameters at time of the scintigraphy, the patients were grouped according to the severity of the scintigraphic abnormalities. We investigated whether the clinical characteristics (demographic data, presence of symptoms, therapies applied) and laboratory parameters were different in these groups. For continuous variables variance analysis, while for categorical variables Kendall's tau-b test was applied. P values below 0.05 were considered statistically significant.

In order to identify the clinical or laboratory indicators with high predictive value for CTD, two patient groups were formed based on the results of two years of follow-up: those for whom the evolution into connective tissue disease could be proved and the others where the diagnosis of CTD could not be established. Individual odds ratio (OR) estimates and their 95% confidence intervals (CI) were calculated for the clinical and laboratory variables, and Fisher's test was applied to calculate significance levels.

The SPSS program package was used for the statistical calculations.

Results:

Clinical data of 145 patients with UCTD

As described above 145 patients were investigated. Clinical and laboratory data of the patients at the study entry are shown in Figure 1. The frequencies of the most important symptoms were the following: polyarthritis in 116 (80%) cases, Raynaud syndrome in 70 (48.3%), dysphagia in 43 (29.6%), xerophtalmia in 38 (26.2%), sclerodactylia in 37 (25.5%), myalgia/myositis and oesophagitis in 36 (24.8%), thrombosis in 34 (23.4%), pulmonary involvement in 30 (20.7%), central nervous system involvement in 28 (19.3%), neuropathy in 24 (16.6%), xerostomia in 23 (15.9%), skin symptoms in 22 (15.2%), serositis in 15 (10.3%) and erosions shown on X-ray films in 12 (8.3%). Regarding the laboratory and immunological alterations,

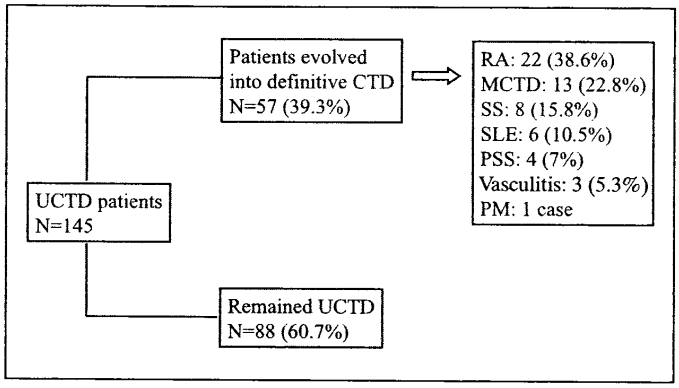

Figure 2. Diagnosis of 57 patients who developed CTD after a two-year follow-up

ANA positivity was found in 70 (48.3%) cases, Waaler-Rose positivity in 58 (40%), elevated CRP level in 52 (35.9%), accelerated erythrocyte sedimentation rate (ESR) and aRNP positivity in 45 (31%), aDNA positivity in 35 (24.1%), aENA in 30 (20.7%), aCL IgG in 29 (20%), aCL IgA in 28 (19.3%), aβ2GP1 IgM in 27 (18.6%), aCL IgM in 25 (17.2%), aβ2GP1 IgG and aSSA in 24 (16.5%), aβ2GP1 IgA in 17 (11.7%), low CH50 in 16 (11%), aSm in 15 (10.3%), aSSB in 14 (9.7%), leucopenia in 11 (7.6%), thrombopenia, aScl70, ANCA each in 8 (5.5%), a Jo1 in 4 and a centromer in 3 cases.

Predictive value of scintigraphy

Esophageal motor abnormality at study entry could be detected by scintigraphy in 66 cases (45.5%) (*Figure 1.*), 47 of whom (71.2%) were without clinical symptoms. Fifty seven (39.3%) of the 145 UCTD patients evolved into a definitive CTD, *Figure 2.*, with 33 (57.9%) of them having positive scintigraphy at study entry. Among the 88 patients who remained in the UCTD stage after two years of follow up, „stable UCTD", 55 had negative scintigraphy (62.5%).

Parameter	*Significance*
ANA	0.006
RASH	0.020
Anti β2 GPI IgM	0.039
Anti-Cardiolipin IgA	0.046
Skin	0.057
WBC	0.067

Table 1. Correlation of various parameters with the scintigraphic positivity

Parameters	*Odds ratio (CI)*	*Fisher*
Xerophtalmia	3.846 (1.769-8.333)	p=0.001
Elevated ESR	2.320 (1.131-4.761)	p=0.027
Erosions	2.500 (1.461-4.273)	p=0.001
Granular ANA positivity	2.865 (1.418-5.780)	p=0.004

Table 2. Correlation of clinical and laboratory parameters with evolution into a definitive CTD. CI: confidence interval (at 95% probability level).

Parameters	*Odds ratio (CI)*	*Fisher*
Nucleolar ANA positivity	138.000 (10.929-1742.456)	p<0.001
Scl 70 positivity	23.167 (1.622-330.868)	p=0.001
Sclerodactyly	9.441 (1.051-93.776)	p=0.050
Waaler-Rose positivity	2.610 (2.118-3.215)	p=0.024

Table 3. Correlation of clinical and laboratory parameters with evolution into scleroderma (PSS). CI: confidence interval (at 95% probability level).

Parameters	*Odds ratio (CI)*	*Fisher*
Erosion	**4.000 (1.712-9.346)**	**p<0.001**
Polyarthritis	2.813 (0.618-12.795)	p=0.167 /n.s./
Xerophtalmia	2.244 (0.871-5.782)	p=0.90 /n.s./

Table 4. Correlation of clinical and laboratory parameters with evolution into rheumatoid arthritis (RA). CI: confidence interval (at 95% probability level).

Parameters	*Odds ratio (CI)*	*Fisher*
Homogenous ANA positivity	168.750 (15.836-1798.212)	p<0.001
Anti SSB positivity	8.818 (1.060-35.397)	p=0.033

Table 5. Correlation of clinical and laboratory parameters with evolution into systemic lupus erythematosus (SLE). CI: confidence interval (at 95% probability level).

The proportion of scintigraphic positivity was 57.9% (n=33) among those patients whose disease evolved into a definitive CTD, while among the „stable" UCTD patients it was 37.5% (n=33). The odds ratio for development of a stable CTD was found to be 2.292 by Fischer's exact test (CI:1.160-4.525; p=0.0178).

Correlations of clinical and laboratory parameters with scintigraphic data

Statistically significant correlation was found between the presence and severity of scintigraphic alterations and the ANA, anti-cardiolipin IgA, anti β2glycoprotein1 IgA and IgM autoantibody positivity as well as the skin symptoms in UCTD patients (*Table 1.*).

Risk factor identification

During the two-year follow-up period 57 (39.3%) out of 145 UCTD patients developed an established CTD (Figure 2.) Among these patients 22 (38.6%) developed RA, 13 (22.8%) (MCTD), 8 (15.8%) SS, 6 (10.5%) SLE, 4 (7%) PSS, 3 (5.3%) systemic vasculitis and 1 PM/DM.

To evaluate the clinical symptoms and laboratory parameters that correlated with and thus had predictive value for the development of a definitive CTD, the odds ratio (OR) values were calculated.

The presence of xerophthalmia (OR: 3.846, CI:1.769-8.333; p=0.001), elevated ESR (OR:2.32, CI:1.131-4.761; p=0.027), erosions on hand X-ray (OR:2.50, CI:1.461-4.273; p=0.001), and granular ANA positivity (OR:2.865, CI:1.187-4.724; p=0.004) were highly predictive of evolution into a definitive CTD (*Table 2.*).

The development of nucleolar ANA positivity /OR: 138.000 (10.929-1742.456); p<0.001/, Scl 70 positivity /OR:23.167 (1.622-330.868); p=0.001/ sclerodactyly / OR: 9.441 (1.051-93.776); p=0.005/, and Waaler-Rose positivity /OR:2.610 (2.118-3.215); p=0.024) were also highly predictive of evolution to PSS (*Table 3.*).

In contrast with some published data [11], there was found no statistically significant correlation between the presence of dysphagia or Raynaud phenomenon and the final outcome.

Although a number of parameters showed OR values above 1, the only significant predictor of evolution into rheumatoid arthritis (RA) was erosion on the hand X-ray /OR: 4.000 (1.712-9.346); p<0.001/). In all other cases the rather wide CI enclosed 1, thus either the scatter was too large or the number of positive cases was too small for the establishment of significant correlations (*Table 4.*).

Parameters	*Odds ratio (CI)*	*Fisher*
Anti ENA positivity	5.529 (1.700-17.985	p=0.006
Granular ANA positivity	4.449 (1.297-15.256)	p=0.016

Table 6. Correlation of clinical and laboratory parameters with evolution into mixed connective tissue disease (MCTD). CI: confidence interval (at 95% probability level).

Parameters	*Odds ratio (CI)*	*Fisher*
Xerostomia	8.194 (2.010-33.404)	p=0.005
Anti SSA positivity	7.679 (1.896-31.255)	p=0.007
Granular ANA positivity	6.772 (1.352-33.921)	p=0.013
Elevated ESR	4.974 (1.185-20.888)	p=0.026
Xerophtalmia	4.694 (3.401-6.493)	p<0.001

Table 7. Correlation of clinical and laboratory parameters with evolution into Sjögren's syndrome (SS). CI: confidence interval (at 95% probability level).

Parameters	*Odds ratio (CI)*	*Fisher*
Leucopenia	16.762 (1.164-24.789)	p=0.015
Skin symptoms	12.200 (0.905-140.895)	p=0.060 /n.s./
Raynaud phenomenon	2.105 (1.768-2.500)	p=0.073 /n.s./

Table 8. Correlation of clinical and laboratory parameters with evolution into systemic vasculitis. CI: confidence interval (at 95% probability level).

Homogenous ANA positivity /OR: 168.750 (15.836-1798.212); p<0.001/, and anti SSB positivity /OR: 8.818 (1.060-35.397); p=0.033/ correlated with the development of SLE (*Table 5.*).
Anti ENA positivity /OR:5.529 (1.700-17.985); p=0.006/, and granular ANA positivity /OR: 4.449 (1.297-15.256); p=0.016/ had predictive values for evolution to MCTD (*Table 6.*).
Xerostomia /OR: 8.194 (2.010-33.404); p=0.005/, anti SSA positivity /OR: 7.679 (1.896-31.255); p=0.007/, granular ANA positivity /OR: 6.772 (1.352-33.921); p=0.013/, elevated ESR /OR:4.974 (1.185-20.888); p=0.026/ and xerophthalmia /OR: 4.694 (30.401-6.493); p<0.001/ were closely associated with the evolution to SS (*Table 7.*).
The patients with leucopenia /OR: 16.762 (1.164-24.789); p=0.015/ were found to be at high risk for development of systemic vasculitis. The correlation with the skin symptoms and with the Raynaud phenomenon tended to be significant but did not reach the statistical significance at p<0.05 (*Table 8.*).
Only one patient had polymyositis after 2 years of follow up, so reliable statistical analysis could not be performed.
Summarizing the aforementioned results, we can state that initial scintigraphic positivity indicates a higher risk for final evolution into a definitive CTD.The positive predictive value of the esophageal scintigraphy was 42.8%, and the negative predictive value was 73.3% for development of any definitive CTD.

Discussion:

The most often used methods for the examination of esophageal motility disorders are radiographic esophageal passage, gastroscopy, 24-hours manometry and pH-monitoring. Radiographic passage studies using gastrographin or barium can depict anatomical alterations, but their sensitivity in demonstration of subtle motility abnormalities is low, the interpretation is subjective, and they have significant radiation burden. Esophagoscopy can show correct anatomical picture of the gastric mucosa and anatomy, but its value in motility disorders is limited. 24-hours manometry and pH-monitoring are highly sensitive, but are not acceptable for most of the patients because of their invasivity [6].
Significant proportion of connective tissue disorders can be characterized by esophageal involvement, but there has not been any study carried out in patients with UCTD. According to several studies, it can occur even in the absence of esophageal symptoms [12], and the dysfunction can precede anatomic or organic alterations.
The detection of esophageal involvement in UCTD patients has multiple significance: *i)* it may contribute considerably to the worsening of quality of life, and the dysfunction of upper sphincter can lead to repeated aspirations, *ii)* several studies refer to myositis in the background of esophageal dysfunction [10, 13, 14] that can be relieved by early corticosteroid treatment, *iii)* the presence of early scintigraphic alterations can have prognostic value in terms of final outcome.
In the present study we analyzed the clinical, laboratory and scintigraphic features of 145 patients with UCTD. According to a recent study [15] the highest probability of CTD development was observed within the first two years after establishing the diagnosis of UCTD, therefore we identified the odds ratio and predictive values for the final diagnosis after two years of follow-up. Among these, 57 (39.3%) patients

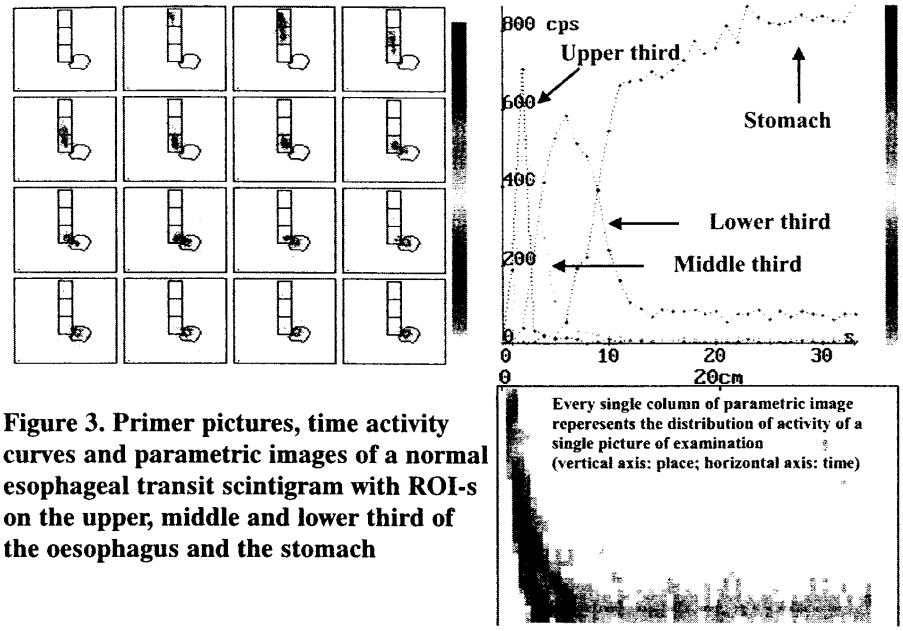

Figure 3. Primer pictures, time activity curves and parametric images of a normal esophageal transit scintigram with ROI-s on the upper, middle and lower third of the oesophagus and the stomach

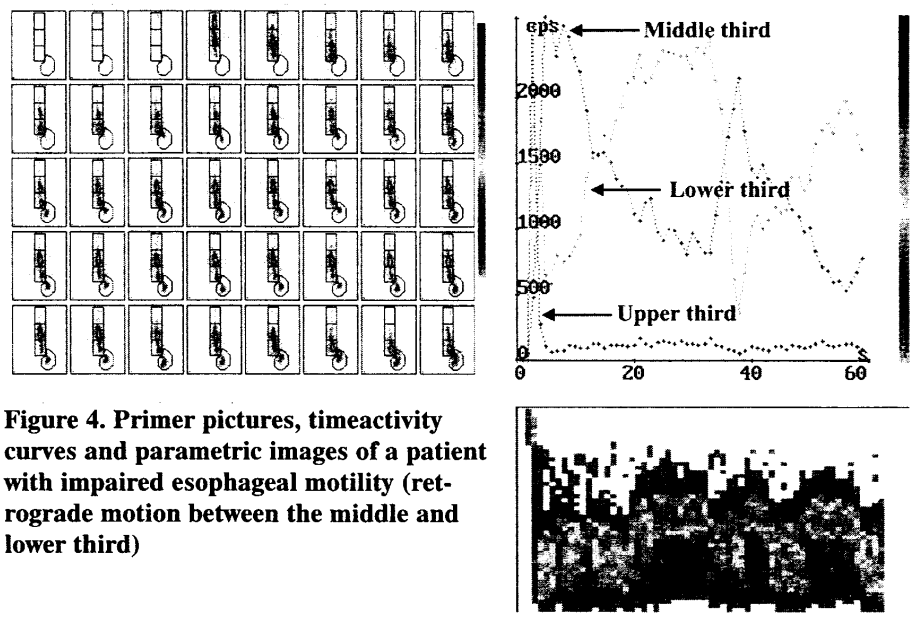

Figure 4. Primer pictures, timeactivity curves and parametric images of a patient with impaired esophageal motility (retrograde motion between the middle and lower third)

went into a definitive CTD during the follow-up period, and almost 60% of them had positive scintigraphy at study entry. Our results showed high prevalence of esophageal involvement in patients with UCTD detected by esophageal scintigraphy. Patients with ANF, anti-cardiolipin IgA, anti β2glycoprotein 1 IgA and IgM autoantibody positivity and skin symptoms are probable candidates for esophageal dysfunction. The early radionuclide esophageal transit scintigraphy has a weakly significant (42.8%) positive predictive value for evolution to definitive CTD. On the other hand, a negative scintigraphic result has a high (73.3%) negative predictive value for development of any definitive CTD.

In patients with UCTD we recommend the performing of esophageal scintigraphy even in the absence of esophageal symptoms, to screen for occult esophageal involvement. Our method is a modified version of esophageal radionuclide transit scintigraphy suggested by other investigators [17, 18], which is well tolerated by the patients because it requires minimal time, and computer data processing is fast [19]. Radionuclide transit scintigraphy is safe, generally available with easy performance, quick, inexpensive method, which can be accomplished in every nuclear medicine laboratory supplied with a gamma camera. Its additional advantage is that it can be performed with a swallowing physiologic material, is reproducible, quantifiable, convenient for the patient, and its radiation burden is very low. Finally, it can be repeated without restraint and (because it is strictly quantitative due to computerized data processing) the individual examinations performed at different times can be compared, and the efficacy of treatment can be measured. According to literature data the sensitivity in the diagnosis of secondary motility disorders is between 44%-92% depending on the patient population, but in certain disorders (for example in achalasia) it can reach even 100%. Specificity varies between 71% and 88% [20].

Most UCTD patients require drug treatment, some of whom can be treated with non-steroid anti-inflammatory drugs, though certain organ manifestations require systemic corticosteroid or in some cases immunosuppressive treatment.

Study limitations

The one possible limitation of this study is that the follow-up period is relatively short to determine the final diagnosis; therefore the further follow-up can improve the statistical power of this study. Moreover the grading of the severity of alterations is somewhat arbitrary, but there is no universally accepted grading system for this purpose.

Conclusion:

Our study shows that patients with abnormal esophageal scintigraphy in the initial period have a significant risk for the evolution to a definitive CTD and probably worse prognosis. Early recognition of esophageal involvement using RETS can help the clinician in the prediction of final outcome.

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„The present is pregnant with the future."

Voltaire