ORIGINAL STUDIES

V.M.Ryzhyk[1]
D.V.Vershynina[1]
O.M.Mykhalchenko[2]
A.V.Ashykhmin[2]
P.F.Dudiy[1]
O.P.Cherepinska[2]
O.V.Gretchyn[3]
[1]*Ivano-Frankivsk National Medical University*
[2]*'Feofaniya' Clinic of the State Department of Affairs, Kyiv*
[3]*Ivano-Frankivsk Regional Clinical Hospital*

DETECTION FREQUENCY AND VERIFICATION IMPORTANCE OF MRT-SYMPTOMS OF JOINT LESION IN EARLY RHEUMATOID ARTHRITIS

Magnetic-resonance tomography (MRT) is used to examine hands in patients with early rheumatoid arthritis (RA). 32 patients meeting the new PA ACR/EULAR 2010 criteria were involved in the study. In all the examined bone edema and synovitis were detected. In 17 patients out of 32 erosions were identified whose presence correlated with the disease activity. Analysis was made of relationship between bone edema, synovitis and erosion diagnostics and seropositiveness as per antibodies to citrullinated peptides. Bone edema, erosions and synovitis are important diagnostically significant MRT-symptoms in case of early RA. Detection of these lesions using MRT at the early stage of the process may play important role in management of these patients and determination of treatment tactics.

Keywords: *early rheumatoid arthritis, MRT, early diagnostics, erosions, synovitis, bone edema, disease activity.*

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most widely spread and gravest chronic inflammatory diseases of man, having high social significance which is attributed to its considerable global prevalence, trend to steady progression and frequent disability, especially in persons of able-bodied age. Prospects of better prognosis in case of RA are directly connected with beginning of adequate basic therapy at early pre-destructive stage of the disease (not later than 3 months after the onset of the disease) therefore new treatment paradigm envisages establishment of RA diagnosis at initial disease stages [2, 20, 23]. At the same time the solution of this task brings considerable difficulties about [5, 21].

The first years of the disease are known to be critical for development and progressing of the pathological process [3]. During the earliest RA period when the process is in a primary, exudative phase the reversion of the disease is essentially higher in view of still insufficiently formed autoimmune mechanisms [4] and absence of pannus – morphological base of articular destruction [1].Further, 50% of maximally pronounced radiological changes (erosions) are observed during the first 2 to 6 years of the disease [22]. Early intrusions with the help of non-biological and biological disease-modifying drugs are extremely important for control of synovitis and bone destruction. The existing RA diagnostic criteria possess insufficient sensitivity (50-70%) regarding early diagnostics of arthritis [9] therefore diagnostic methods using magnetic-resonance tomography (MRT) allowing to early visualize the RA pathognomonic symptoms (synovitis, bone marrow edema, erosions) is an important tool of early and differential RA diagnostics [6, 25]. Bone edema, synovitis and erosions which are registered in

patients with up to 12-month disease duration are regarded as important signs of aggressive progressing RA course and require fast administration of disease-modifying drugs [11, 19, 24]. Ideal attainment of the best treatment results and possible (the longest possible) remission without structural affections requires administration of these drugs at pre-erosive stage of RA [12, 17]. In this connection the role of MRT increases for early visualization of changes at early stage of RA.

The purpose of this study is to estimate diagnostic possibilities of MRT in early diagnostics of RA in the cohort of patients with articular syndrome having up 1 year duration, and detection of pathognomonic symptoms with the help of enhanced 1.5T MRT.

SUBJECT AND METHODS OF STUDY

32 patients with RA diagnosis (according to ARC/EULAR 2010 classification criteria) were under observation. Average age of patients: 29.3+/-6.7 years. In all cases the duration of articular syndrome was <12 months, in the average: 8.2+/-2.6 months. Women adequately prevailed among the examined persons: 25, men: 7. Each patient was examined by rheumatologist; clinical features of RA course included determination of morning stiffness duration (in min.), total number of inflammatorily changed (swollen) and painful joints, assessment of pain syndrome intensity using visual analog pain scale (in cm). Laboratory examination included complete blood count with erythrocyte sedimentation rate (ESR), determination of C-reactive protein concentration, rheumatoid factor, antibodies to cyclic citrullinated peptide (anti-CCP) and cyclic modified vimentine (anti-CMV). To assess the disease activity, the generally accepted DAS28 score was used [26]. 14 persons were seropositive by rheumatoid factor; 18 – seropositive by anti-CCP, 25 – by anti-CMV.

MRT of dominant hand was made in *Feofaniya* Clinic on the *Siemens MAGNETOM Espree* high-field MR-tomograph with 1.5 T magnetic field induction. The wrist was in neutral position, parallel to the table plane, hand with straightened fingers – in the position of pronation. In such position the hand was fixed by rear cushions and side rollers to avoid movement artifacts and picture distortion. Centering was oriented to the area of the wrist bones proximal row. To examine the state of all the structures belonging to the area of the wrist joint, wrist and fingers, the picture was made in frontal, sagittal and axial plane, thickness of partitions: 3 mm, field of vision (FOV): 9 to 12 cm. The study was made with intravenous introduction of *Megarey* contrasting agent (*Dong Cook Pharmaceutical Co. Ltd.*, Korea) 1 ml of which contains 469.01 mg gadolinium-diethyleneamine-pentaacetic (Gd-DTPA), on the basis of 0.1 mmoll per 1 kg patient mass.

The examination protocol took into consideration the following images (33): axial and coronal STIR-images with 2500; 60; 160 (time of repetitions ms/echo-frequency, ms/inversion, ms), with 3 mm partition thickness, 0.3 mm intersection clearance, 256x256 image matrix; T1-33 spin-echo in coronal projections with 500; 16 (time of repetitions, ms/echo-frequency, ms) with 3 mm partition thickness, 0.3 mm intersection clearance, 256x256 image matrix; T1-FS (fat suppressed)-33 spin-echo in coronal projection with 500; 16 (time of repetitions, ms/echo-frequency, ms) with 3 mm partition thickness, 0.3 mm intersection clearance, 256x256 image matrix before introduction of the contrasting agent, and coronal and axial projections immediately after introduction of Gd-DTPA. The contrasting substance was intravenously introduced on the contralateral arm.

The hand and wrist joints were assessed OMERACT PA MRT score separately for assessment of bone edema, synovitis and erosions [7, 8, 19]. The STIR-images

were assessed to detect osteitis, and T1-33 fat suppressed – to assess synovitis and erosions. Since the smallest partition possible was 3 mm, the erosions were assessed as the bone area with irregular bone contour [13]. Intravenous enhancement with the help of Gd-DTPA drugs allows to more adequately assess synovitis and visualize bone erosions.

Statistical processing of the obtained results was made using PC with *Stratgraphics Plus v3.0* software. The average value, standard errors, difference reliability as per Student's test were assessed, paired correlation analysis was made. The results are represented as M+/-m.

STUDY RESULTS

Clinical profile of the examined patients is given in table 1.

Table 1

Clinical profile of 32 examined patients with early RA

| Clinical/laboratory parameters	Early RA (n=32)
Age, years	29.3+/-6.7
Women/men	25/7
Disease duration, months	8.2+/-2.6
DAS28 disease activity, points	5.4+/-1.2
C-reactive protein, mg/ml	24.3+/-8.4
Rheumatoid factor (+)	14/32
Anti-CCP (+)	18/32
Anti-CMV (+)	25/32
Anti-CCP (+) and anti-CMV (+)	15/32
Anti-CCP (-) and anti-CMV (-)	4/32

The most frequently detected in the examined patients were bone erosions (fig.1, 3), bone marrow edema (fig.2), synovitis (see fig.3, fig.4). There were no reliable correlations between the detected MRT-symptoms and duration of morning stiffness, total count of swollen and painful joints, intensity of pain syndrome as per VAS score, and ESR. The examination results are given in table 2.

Fig.1. Coronal T1-vibe-FS-33 plane. The arrows show condylus erosion of III and IV metacarpal bones as well as capitalum and unciform bone

Fig.2. T1-FS-33, hand coronal projection. Condylum erosion of elbow bone (white errow) and pronounced synovitis of wrist joint (rosy arrow)
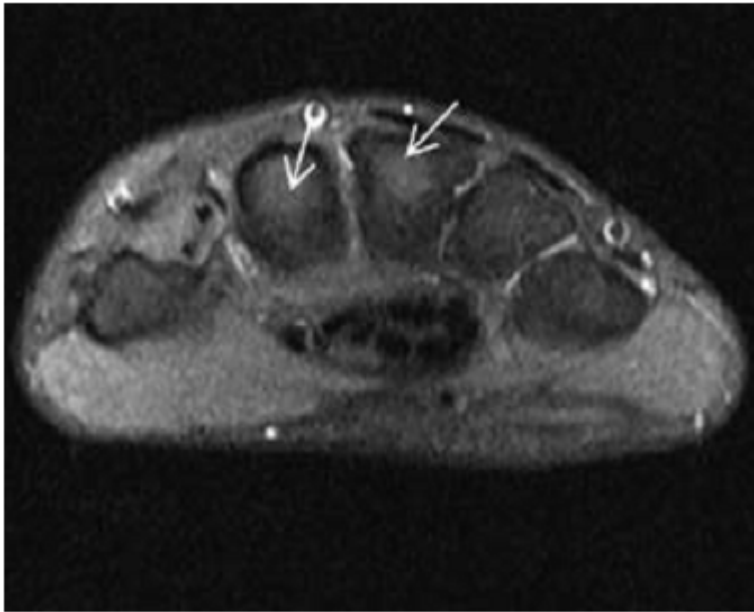
Fig.3. T1-33, axial projection. Bone edema of condyles of metacarpal bones – change of MRT signal (shown by arrows)

Fig.4. Sagittal projection, T1-33, pronounced synovitis signs of wrist joints with significant accumulation of the contrasting agent (rosy arrows) and bone edema signs (white arrow)

Table 2

Incidence of edema, erosion and synovitis in the examined patients with early RA

MRT-symptom	Number of patients, n
Bone marrow edema (osteitis)	32/32

• Wrist	30/32
• condyles of wrist bones	27/32
• condyles of bones which make proximal interphalangeal joint	16/32
Erosions	17/32
• wrist bones	11/32
• condyles of metacarpal bones	6/32
• condyles of bones which make proximal interphalangeal joint	5/32
Synovitis	32/32
• wrist bones	28/32
• MTP joints	19/32
• Proximal interphalangeal joints	18/32

All the patients were diagnosed osteitis and synovitis, with erosions being verified in 17 examined persons only. The most frequently detected were edema of wrist bones (in 30 patients), condyles of metacarpal bones (in 27 patients), wrist synovitis (in 28 patients). As for erosions, the most frequently diagnosed was usuration of wrist bones (in 11 patients), and less frequently detected were erosive lesions of condyles of metacarpal and phalangeal bones. We should note that presence of synovitis and osteitis was not dependent on the disease activity whereas bone erosions were more often detected in the patients with high disease activity. Thus, positive correlation was established between presence of erosions and DAS28 – $r=0.64(p<0.01)$.

We also analyzed relationship between detected MRT-symptoms and sero-quality of patients – seropositiveness as per anti-CCP and anti-CMV. The obtained results are given in table 3.

Table 3

Erosions, synovitis and bone edema (osteitis) detection frequency against seropositiveness by anti-CCP and anti-CMV

Parameter	Erosions, n (%)		Synovitis, n (%)		Bone edema, n (%)	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**
Anti-CCP positive	10(55.6)	8(44.4)	16(88.9)	2(11.1)	18(100)	0
Anti-CCP negative	4(28.6)	10(71.4)	8(57.1)	6(42.9)	12(85.7)	2(14.3)
Anti-CMV positive	13(52)	12(48)	25(100)	0	25(100)	0
Anti-CMV negative	1(14.3)	6(85.7)	3(42.8)	4(57.2)	7(100)	0
Anti-CCP, anti-CMV positive	14(93.3)	1(6.7)	15(100)	0	15(100)	0
Anti-CCP, anti-CMV negative	0	4(100)	2(50)	2(50)	3(75)	1(25)

In all the patients, seropositive by both markers, erosions, synovitis and osteitis were detected and in seronegative patients no erosions were detected, and synovitis and osteitis were diagnosed with lower frequency. In general, as the obtained results show, in the patients, positive by anti-CCP or anti-CMV, erosions, synovitis and bone edema were observed more often than in case of seronegativeness by one of these parameters. To assess synovitis and erosion intensity OMERACT system was used and assessment depending on seropositiveness by anti-CCP or anti-CMV was made. So, in case of positive anti-CCP the synovitis score was 5.16+/-1.12 points, in case of negative anti-CCP – 2.84+/-0.87 points (p<0.05); score of erosions – 3.28+/-0.66 points in case of positive anti-CCP against 1.92+/-1.06 points in case of negative one (p<0.05). In

case of positive anti-CMV the synovitis score was 6.03+/-2.11 points, in case of negative anti-CMV – 3.24+/-1.87 points (p<0.05). As for the score of erosions there were no adequate differences between groups with positive and negative anti-CMV: 4.12+/-2.67 points against 2.13+/-2.04 points (p>0.05). The highest scores of synovitis and erosions were observed in case of seropositiveness by the two citrullinated antibodies. Thus, in case of positive anti-CCP and anti-CMV the synovitis score was 7.93+/-2.75 points, and in case of negative antibodies – 4.12+/-1.67 points (p<0.01). The score of erosions was 4.33+/-1.84 points in case of seropositiveness by the two markers, in case of seronegativeness by anti-CCP and anti-CMV no erosions were detected.

DISCUSSION OF RESULTS

In this study the OMERACT PA MRT score system was used for detection of erosions, synovitis and bone edema in patients with early RA (disease duration up to 12 months) as well as for determination of differences depending on different immunological variants of RA course and on disorder activity. MRT of hands and wrist is mainly used to determine the rate to which the joints are involved in the pathological process. Most of the studies dealt with the patients having the established RA diagnosis and at the late stages of the process. Only a few studies were made in the patients with very early RA – with articular syndrome duration <4 months. With such patients in 45% of cases erosions of bone surfaces were detected [15] but half of them received treatment with disease-modifying drugs. In fact erosion detection rate at RA early stages is much higher. Thus, in the study of P.E.Kosta et al. (2011)[10] the erosion frequency in the patients with disease duration ≤3 months was 96.15%, and in case of disease duration >12 months the erosions were detected in all (100%) the examined patients. The difference in verification of erosions may be probably attributed to early beginning of treatment which appreciably restrains the erosive process and early administration of biological therapy conduces to their healing. The previous studies showing very early detection of citrullinated peptides in potential patients allowed to conclude that the pathologic rheumatoid process starts long before the first clinical symptoms appear [18]. Our study corroborates this hypothesis because all the patients were diagnosed bone edema and synovitis, and erosions – in 17 out of 32 examined persons. Especially important MRT-symptom is bone edema because it may be detected at any stage of the disease and mark its more aggressive course [14]. The bone edema presents manifestation of real inflammatory process in the bone and at the same time that of pre-erosive lesion which may be reverse in case of early start of disease-modifying therapy. Synovial membrane is the main base of immunological conflict therefore synovitis detection at the early stage of RA is pathognomonic and important. The bone erosions are known to be formed due to direct 'sprouting' of pannus into the bone and also due to elevated concentration of pro-inflammatory cytokines which are produced in excessive number by the inflamed synovial membrane. The pronounced synovitis may be also regarded as preliminary stage of the erosive process. Therefore unlike with radiological erosions which reflect bone lesion which has already occurred, the bone edema and synovitis present early inflammatory infiltrates and may be the cause of erosions [14].

In our study the erosions were also with higher frequency detected in the patients with higher disease activity although the bone edema and synovitis were detected with the same frequency at different parameters. But the study [16] made recently on a small group of patients (n=18) showed correlation between synovitis and DAS28 (the study was made on the set with 3T magnetic field induction using T1-33 dynamic contrast enhancement). To estimate advantages of MRT-examination at the early stages of RA further studies are needed.

CONCLUSIONS

1. Bone edema, erosions and synovitis are early MRT-symptoms of RA. Taking into consideration that in case of RA these are the hands that are affected most frequently, MRT of this area is important for assessment of involvement of articular structures in the pathological process.
2. Simultaneous presence of anti-CCP, anti-CMV and typical changes on hand MRT in the patients in the disease debut is a marker of the graver, prognostically unfavorable RA course which requires urgent active treatment measures.
3. Detection of MRT-symptoms of RA (bone edema, synovitis, erosions) in seronegative patients allows to suspect RA at early stage and provide clinical/laboratory monitoring of RA course in such patients.

Prospects of further studies are in extension of database of patients with early RA which would allow to establish mechanisms and correlations between clinical and between instrumental symptoms and identify pathognomonic MRT-symptoms in patients with very early RA (disease duration ≥3 months)

BIBLIOGRAPHY

Address for correspondence:

Ryzhyk Valery Mykolayovych
76019, Ivano-Frankivsk, vul.Galytska, 2
Ivano-Frankivsky natsionalny medychny unversytet, kafedra radiologii ta radiatsiynoi medytsyny